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SURGERY

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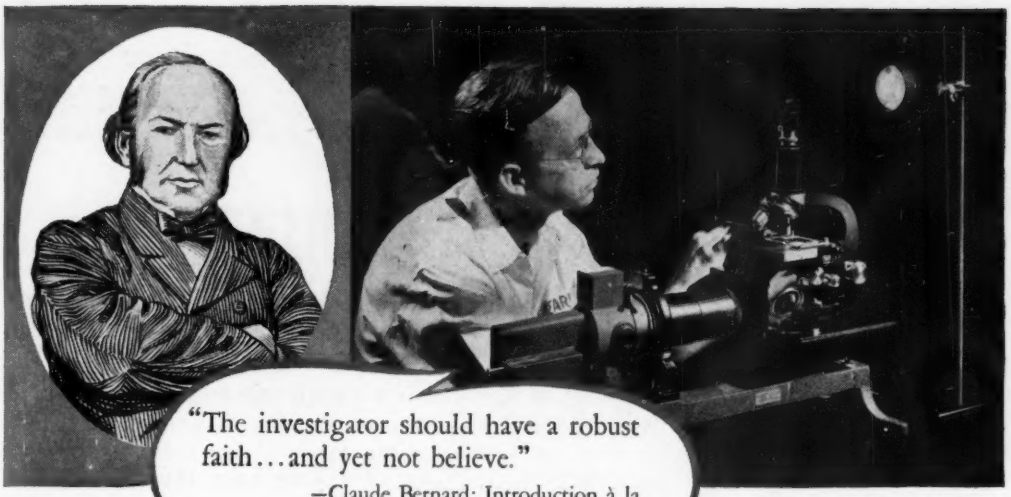

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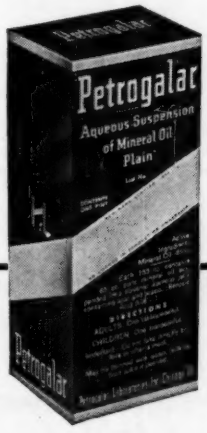

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SURGERY

VOL. 12 DECEMBER, 1942 NO. 6

Original Communications

LIGATION OF THE PATENT DUCTUS ARTERIOSUS

A REPORT OF THE RESULTS IN SEVEN CASES

GEORGE H. HUMPHREYS, M.D., NEW YORK, N. Y.

(From the Department of Surgery, Babies Hospital, and of the College of Physicians and Surgeons, Columbia University)

THE possibility of successfully obliterating by surgery a ductus arteriosus which has remained patent beyond the neonatal period was established over two years ago by Gross and Hubbard. The number of reported cases in which the procedure has been carried out is, however, still small. As a result the risks of the procedure as well as its late results are still a matter of some uncertainty, and the indications for attempting it are not yet generally agreed upon. Since clarification of these points can come only through accumulation of experience, it seems worth while to present case reports, to review the reasons for operating, and the results obtained.

All of these patients were children between 9 and 13 years of age. They were selected from a group of twenty children in which the diagnosis of patent ductus arteriosus without other cardiovascular anomaly had been made, which had been referred for consideration of surgery. All were thought to show evidence that the continued patency of the ductus was resulting in deleterious effects, and two had evidence of complicating subacute blood stream infection. The first patient was not only poorly developed and nourished, but had had evidence of diminished cardiac reserve for several years, with one episode of mild congestive failure. The second patient also showed diminished cardiac reserve but without failure, and in addition had a long record of recurrent respiratory infection, with poor appetite and nutrition though normal development. The third patient had a similar record of repeated respiratory infection, poor appetite and nutrition, but normal development and little or no diminution of cardiac reserve. The fourth and fifth patients

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both showed marked retardation of growth and development though their nutrition and cardiac reserve were not conspicuously affected. The fifth patient developed a subacute blood stream infection and a recurrence of patency of the ductus, for which a second operation was performed. The sixth patient showed poor nutrition, delayed growth and development, and frequent respiratory infections, but little diminution of cardiac reserve. Subacute blood stream infection was the primary indication for operation on the seventh patient, who otherwise showed poor nutrition but little delay in growth and no appreciable diminution of cardiac reserve. The factors which influenced the decision to operate are summarized in Table I.

The physical signs and data obtained from x-ray, electrocardiographic and electrostethographic studies, on which the diagnosis in each case was based, are described in the individual case histories. It is interesting to note that in several cases, one or more of the usual diagnostic criteria were absent, yet in every child explored a patent ductus was found. A low diastolic pressure was the most consistent finding. Studies of pulmonary ventilation and cardiac output were also made in several of these patients and will be reported in a separate paper. Associated skeletal anomalies were present in three children, and a congenital squint and torticollis were present in another.

TABLE I

SUMMARY OF FACTORS INFLUENCING DECISION TO OPERATE

PATIENT	CARDIAC FAILURE	DIMINISHED CARDIAC RESERVE	CHRONIC MALNUTRITION	DELAYED GROWTH AND DEVELOPMENT	REPEATED RESPIRATORY INFECTIONS	SUBACUTE BLOOD STREAM INFECTION
R.R.	+++	++++	++++	+	±	0
R.B.	±	+++	+++	0	++++	0
F.F.	±	+	++	±	++++	0
J.B.	0	0	++	++++	±	0
T.Y. a.	0	0	+	++++	±	0
R.H.	0	0	+++	+++	+++	0
T.Y. b.	0	0	+++	++++	±	*Staph. aureus*
J.M.	0	±	+++	±	++	*Str. viridans*

CASE REPORTS

CASE 1.—R. R. was born at home on March 22, 1928, a normal full-term delivery. She was the sixth of eight children of an Italian laborer, whose wife is also his first cousin. Both parents are in good health. The third child, aged 18 years, is an imbecile; the seventh child, aged 8 years, has celiac disease; the eighth child died at three months of unknown cause; the other four children are well and normal as far as known. There is no known history of tuberculosis or heart disease in the family, but the parents are vague as to the health of relatives in Italy.

Her neonatal period was uncomplicated. Shortly after her birth her mother was told that the baby had heart trouble for which nothing could be done. In spite of this her early childhood development was not retarded; she had no blue spells, no cardiac symptoms, and was able to keep up in school. She went through measles and chicken pox without sequelae, and had no joint pains or chronic fever. Until the present illness she had had no injuries or operations.

Beginning in 1934, at about the age of 6, she began to find it difficult to keep up with other children at play. She had occasional epistaxes and noticed increasing dyspnea and precordial discomfort associated with palpitation on exertion. Because of these symptoms during the three years prior to admission she had been followed in the cardiac clinic of the Greenpoint Hospital, and had been put in a special cardiac class at school.

In March, 1939, she first noticed ankle edema, with tenderness on pressure on the left. She was admitted to Greenpoint Hospital and while there an abscess formed at the tip of her left great toe. This broke spontaneously, discharged pus for a short time, then healed. She was transferred on May 25, 1939, to Kings County Hospital. Physical examination at this time showed marked malnutrition, underdevelopment, and a chest deformity of pigeon breast type, without other evidence of rickets. There was a continuous precordial thrill and loud continuous murmur with systolic accentuation. Her arterial blood pressure was 96/38 and her venous pressure 170. The liver could be felt one and one-half fingers below the costal margin. X-ray of her chest showed an enlarged left auricle and ventricle and accentuated conus.

On June 21, 1939, she was discharged for convalescence to Seaside Hospital, with a diagnosis of patent ductus arteriosus. She remained there, in bed, until Aug. 27, 1939. During this time she ran an intermittent low-grade fever and showed a constantly elevated sedimentation rate (about 30 mm. per hour). Wassermann was negative; Mantoux, positive. Urine and blood counts were not remarkable. The foot showed variable swelling and tenderness but never redness, heat, or purulent discharge. Other findings confirmed those noted at Kings County Hospital. She was discharged, Aug. 28, 1939.

The patient was admitted to Babies Hospital on Sept. 11, 1939, for ligation of the patent ductus. Examination showed: Temperature 100°; sedimentation rate, 49 mm. per hour; white blood count, 20,950; urine, negative; Mantoux, negative 0.01 Gm., positive 0.1 Gm.; blood pressure, 95/45 (right arm); venous pressure, 95. She was a poorly developed girl, showing pronounced malnutrition, adenoid facies, and a narrow chest with pigeon breast deformity of the sternum. Her feet were flat and of peculiar shape; there was a scar on the terminal phalanx of the left great toe and the left ankle was slightly edematous. Her heart was slightly enlarged with an almost continuous thrill over the whole precordium, most pronounced over the third left interspace. Sounds over the right base were of fair quality, elsewhere they were obliterated by a loud "machinery" murmur with systolic accentuation. The systolic murmur was transmitted to neck and back. No cyanosis or clubbing were present.

X-rays of chest showed prominence of pulmonary conus and accentuated bronchovascular markings. Kymography and fluoroscopy showed pulsations of hilar shadows. X-rays of feet showed bilateral congenital anomalies of the third metatarsals. The right astragalus showed deformity and periosteal reaction of obscure etiology. Electrocardiogram showed no significant alteration from normal.

Operation was done Oct. 3, 1939. A ductus about 1 cm. in diameter and 0.8 cm. long was doubly ligated according to the technique described by Gross. Endotracheal ether anesthesia was used.

Postoperatively her immediate response was excellent. Twenty-four hours after operation she developed marked dyspnea due to laryngeal and tracheal edema associated with profuse mucoid discharge. X-rays showed some density at left base, probably atelectasis. These symptoms subsided during the next three days. Her temperature varied up to 102° for the first four days, was normal after the fifth. The wound healed by primary union, stitches being removed on the sixth day. She was up on the seventh day, home on the twelfth. On discharge her heart showed

complete absence of the previous thrill and murmur. X-rays showed disappearance of the pulmonary conus bulge, no pneumothorax, slight density at left base suggesting residual atelectasis, and bronchovascular markings less dense. X-rays of feet showed a new lesion involving the first left metatarsal. She was discharged, walking, Oct. 15, 1939.

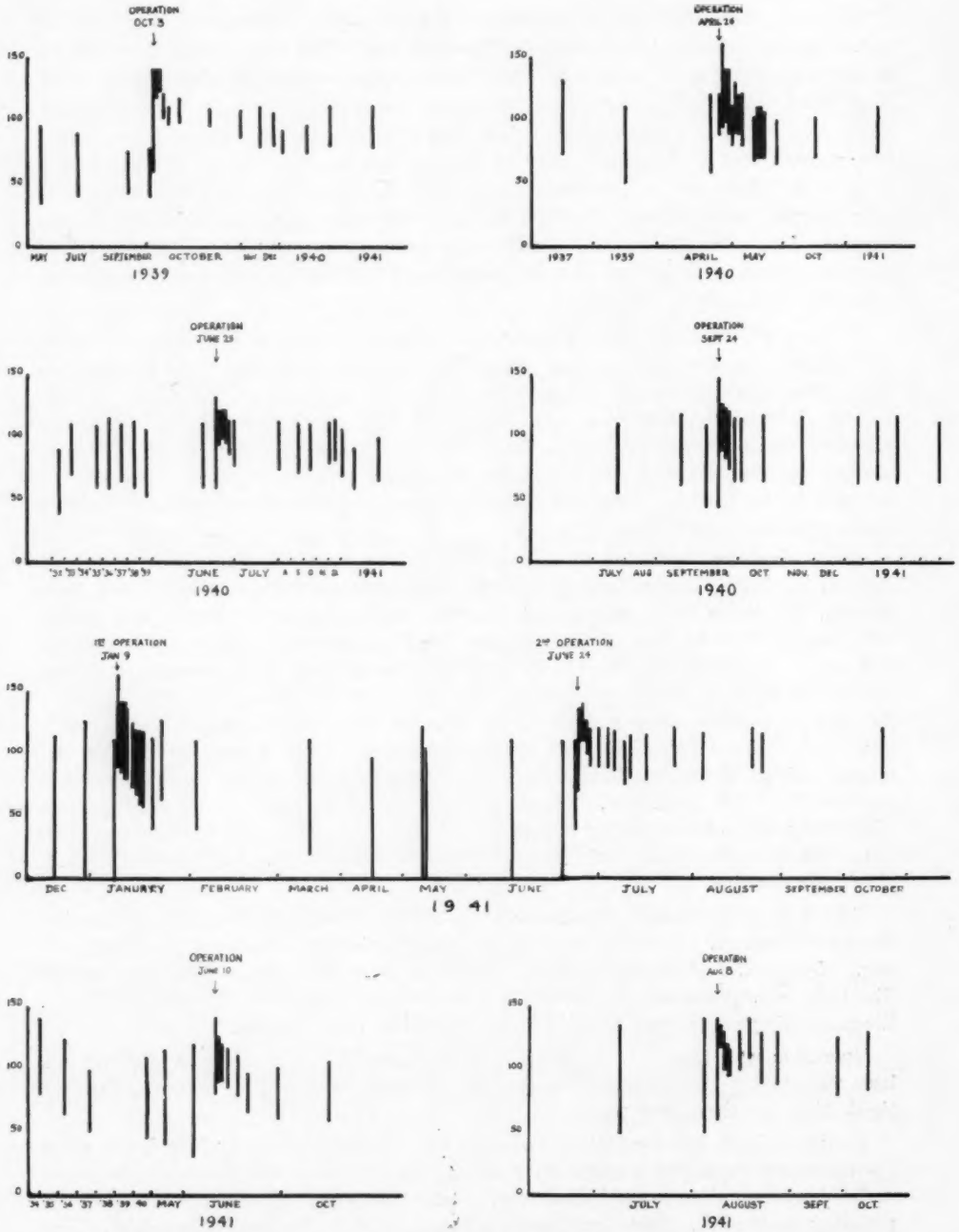
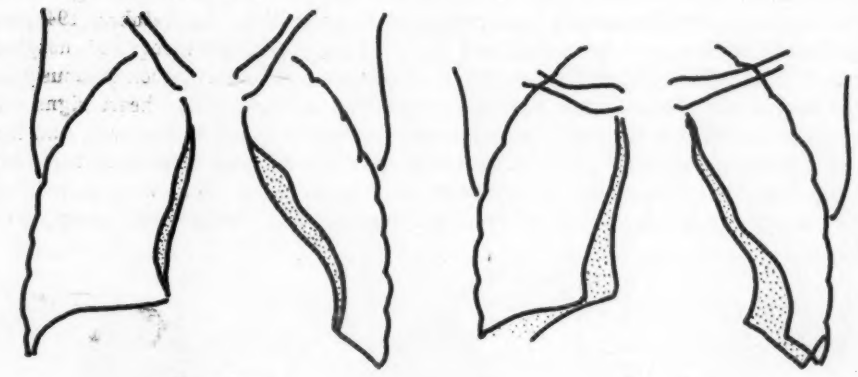
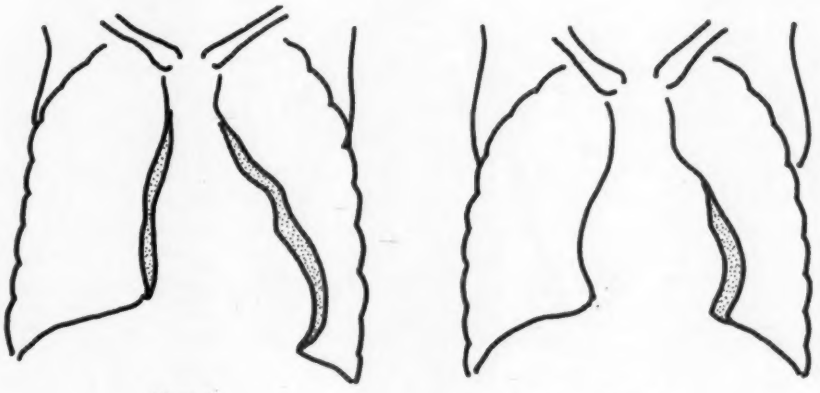


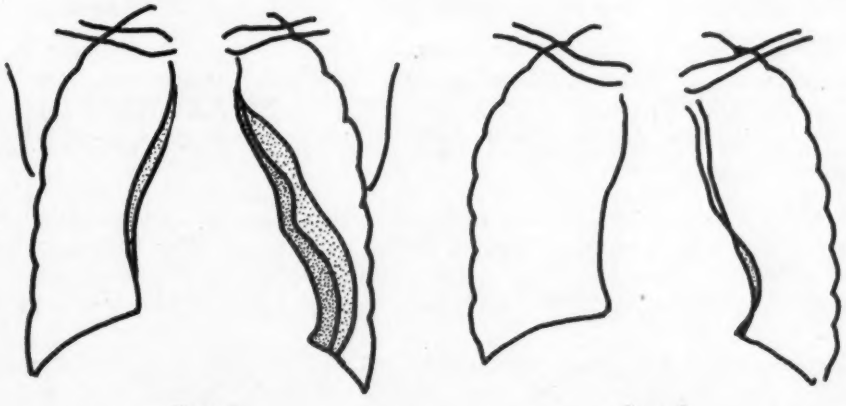
Fig. 1.—A chart of blood pressure readings before operation, in the immediate postoperative period, and in the follow-up period showing the response to eight ligations in seven patients. In every instance both systolic and diastolic pressures rise abruptly following ligation, then fall during the postoperative period to a new level, with pulse pressure lower and diastolic pressure higher than before operation.



Case 1. Case 2.



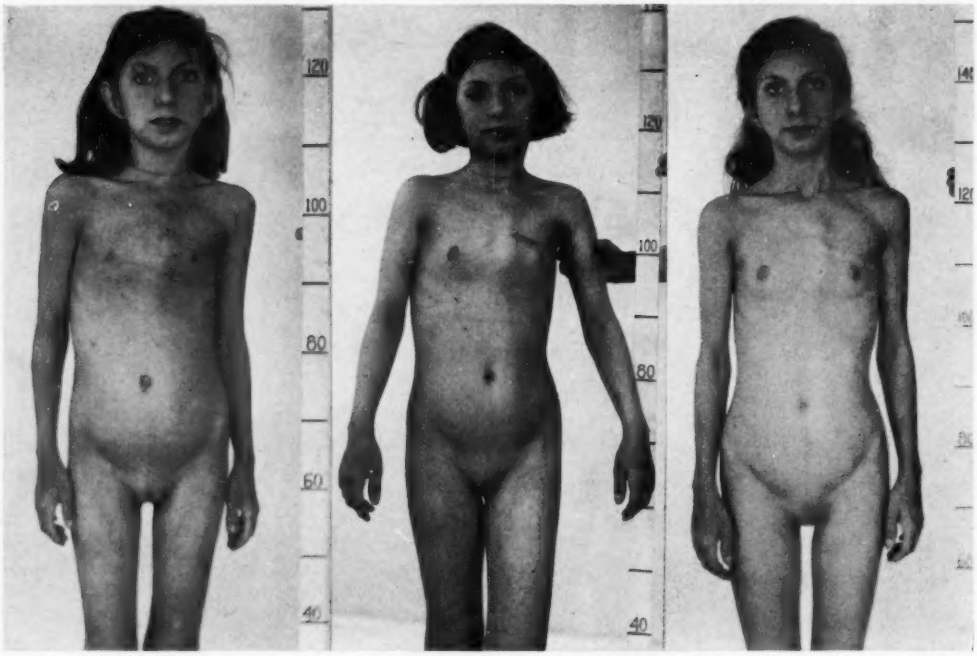
Case 3. Case 4.



Case 5. Case 7.

Fig. 2.—Tracings of roentgenograms to show changes in the size and shape of the cardiac shadow following ligations in six patients. The most striking change is a decrease in the left ventricular shadow. The "pulmonary conus" shadow disappeared in Case 1, and decreased in size in Cases 2 and 5, but in Case 3 it became more conspicuous and in Case 4 it appeared only after ligation. Case 7 showed none of the changes associated with a patent ductus, and changed very little following ligation.

From Nov. 1, 1939, until Sept. 1, 1940, she was admitted and discharged four times due to difficulties related to her metatarsal anomalies. In October, 1940, an imperforate choana was corrected, and in 1941 her feet again required hospital care. During this period she grew rapidly in height and improved conspicuously in vigor though her nutrition was not well maintained at home. Her heart signs did not change, a short, soft systolic murmur was constantly heard at the base, and her blood pressure remained at 110/80. Because of the difficulties related to her feet, activity was somewhat restricted for much of this time, but there were periods of vigorous activity which caused no cardiac symptoms, nor evidence of decompensation.



A. *B.* *C.*

Fig. 3, Case 1.—*A*, Ten days after operation; note poor nutrition, apathetic attitude, and expression. *B*, Six months after operation; note great improvement in nutrition and gain in height in spite of the fact that disease of the tarsal bones had kept her hospitalized. *C*, Two years after operation; note increase of 20 cm. in height though nutrition has not been well maintained. The left mammary gland is developing normally under the scar.

CASE 2.—R. B. was born at home on Sept. 15, 1928, a normal full-term delivery. He was the fourth of seven children of Italian parents. An older brother and a sister suffer from rheumatic heart disease and all members of the family became infected with trichina in 1934. Otherwise the siblings and parents are in good health.

His neonatal period passed uneventfully and he developed at a normal rate, though a diagnosis of congenital heart disease was made, because of a cardiac murmur, at the age of three months. He was followed in the cardiac clinic of the Nursery and Child's Hospital from this time until the age of four years when he was transferred to the Bellevue Hospital cardiac clinic.

During the next five years he was seen frequently with respiratory infections which on three occasions were of sufficient severity to require admission.

On Jan. 22, 1937, he was admitted because of fever, dyspnea, fatigue, joint pains, and general malaise. He appeared acutely ill, pale and slightly icteric, with

dyspnea, orthopnea and generalized lymphadenopathy. His heart was enlarged outward and downward and showed marked tachycardia, gallop rhythm, a thrill over the entire precordium, and a machinery-like murmur at the base. At this time the joint pains, together with an x-ray cardiac shadow which was not considered typical of patent ductus, and the fact that both systolic and diastolic murmurs could be heard at the apex raised the question of a possible superimposed rheumatic heart disease. However, laboratory evidence failed to substantiate this. He improved rapidly on bed rest and after being allowed up a week after admission it was found that arch supports relieved his leg pains.

During the next two years his cardiac function remained much diminished, so that he could not climb stairs without marked dyspnea and was able to play no active games. He attended a cardiac class in school and efforts to maintain nutrition and general resistance were unremitting. In spite of this, though he grew and developed normally for his age, his weight became increasingly below average for his height and age.

He was admitted to Bellevue Hospital on Dec. 26, 1939, for ligation of the patent ductus. Examination showed: Temperature, 99°; pulse, 100; respirations, 22; blood pressure, 110/50; height, 5 feet 4 inches; weight, 87 pounds. He was a swarthy boy, underweight but not undersize for his age, who showed some persistent mucopurulent postnasal discharge. There was no cyanosis, clubbing of fingers, edema, or other abnormality of abdomen or extremities. His heart showed diffuse enlargement with the maximum impulse in the anterior axillary line in the fifth intercostal space, forceful and much more prominent than normal. A systolic thrill was present at the second left intercostal space where a loud machinery-like murmur involving systole and diastole was heard. This murmur was transmitted throughout the precordium. The pulmonic second sound was loud.

X-rays showed diffuse enlargement in all diameters, most marked of the left ventricle. The left border was straight and steep, and both lungs showed congestion which did not show "hilar dance" on fluoroscopy. The superior mediastinum appeared broadened due to a prominent vena cava and ascending aorta, and in oblique views the pulmonary conus appeared prominent but not the left auricle. Electrocardiograms showed no significant changes, and electrostethograms showed a continuous irregular murmur present throughout systole and diastole, heard with greatest intensity at the pulmonary area and transmitted to the apex.

Operation on this admission was deferred because on Jan. 2, 1940, he developed an acute upper respiratory infection and on January 22, fever and deep jaundice, presumably catarrhal. This began to clear on January 29, and he was discharged to a convalescent home on Feb. 7, 1940.

He was readmitted to Bellevue Hospital on April 23, 1940, for ligation of his patent ductus. His condition was essentially unchanged except for some gain in weight and minimal evidence of respiratory infection.

Operation was done April 26, 1940. A ductus about 1 cm. in diameter and 5 mm. long was exposed and doubly ligated with heavy braided silk according to the technique of Gross. Intratracheal ether was used and the patient stood the procedure well.

Postoperatively he was comfortable though somewhat dyspneic for the first two days during which his temperature fluctuated up to 102°. On the second day x-ray showed evidence of pleural exudate and 550 c.c. of bloody fluid was withdrawn on thoracentesis. The following day 200 c.c. more were withdrawn. On the fourth day his temperature rose to 103.2°, he appeared acutely ill, and x-rays showed density of the midthird of the left lung and widening of the mediastinum. During the next forty-eight hours 9 Gm. of sulfapyridine were given and his temperature returned to normal, where it remained. On the seventh day he appeared slightly icteric, but his general condition had much improved. His wound had healed by primary union.

On the tenth day he was given a transfusion of 250 c.c. and this was repeated on the twelfth day, as his blood count remained at 2,400,000. Following this he improved steadily and by the eighteenth day was walking. X-rays during the fourth week showed some persistent atelectasis or fluid in the left lung field, as well as widening of the mediastinal shadow, but he felt increasingly well, and auscultation and electrostethogram showed no evidence of the previously present murmurs. He was discharged, weighing 93 pounds, on his twenty-seventh postoperative day, May 23, 1940.

During June he remained apprehensive in attempting activity and was sent to the posture clinic for correction of a scoliosis acquired postoperatively. During the summer he was allowed full activity in a boys' camp where he found that his previous limitations on exertion were no longer present, and made a striking improvement in nutrition and vigor.

On Oct. 10, 1940, he had gained thirteen pounds and grown one inch in the five months since operation. His heart shadow on x-ray was normal in size and contour, and examination revealed no murmur. He was able to keep up with normal children in active play without signs of dyspnea or fatigue.

One year after operation he had gained another three pounds and another inch. He was leading an entirely normal life.

CASE 3.—F. F. was born in Harlem Hospital on Oct. 8, 1928, a normal full-term delivery. He was the first of three children of Puerto Rican parents. An extensive hemangioma involving one arm is present in one sister, otherwise both parents and siblings are in good health and no familial diseases are known.

His neonatal period was uneventful and he gained weight and developed normally during the first fifteen months, being breast fed for this period. At ten months he was examined by a doctor because of a respiratory infection and a heart murmur was found. During the second year he seemed to tire easily at play and had frequent respiratory infections. Cyanotic spells were absent.

On Oct. 18, 1930, he was admitted to Babies Hospital with signs of chronic bronchitis and a heart enlarged to percussion with a very loud continuous harsh murmur in the left second interspace, transmitted to the back. There was some asymmetry of the chest with prominence just to the left of the sternum. In spite of a great deal of violent screaming, no cyanosis was present. X-ray of the chest showed cardiac enlargement only; electrocardiogram was negative, blood pressure 90/40. He was followed at irregular intervals in the cardiac clinic where it was noted that he tended to remain underweight and to have many colds.

During the next six years he was admitted to Babies Hospital on four occasions; once because of a gangrenous appendix, once for a severe respiratory infection, once for intestinal obstruction, and finally for tonsillectomy in the hope of relieving his frequent respiratory infections.

In 1937 his failure to gain weight became a difficult problem because of the emotional instability of his parents. Mild frequent colds continued. During 1938 and 1939, he improved and was in fair condition. The precordial bulge and thrill, the coffee-mill murmur in the pulmonic area, and the slight cardiac enlargement persisted, but he was able to shift from a special cardiac class to a parochial school where he got along well without physical restrictions.

He was admitted to Babies Hospital for ligation of the patent ductus on June 22, 1940. Examination showed: Temperature, 101°; pulse, 96; respirations, 20; blood pressure, 110/70; height, 4 feet 8 inches; weight, 71 pounds. He was a swarthy boy of asthenic habitus who, except for his chest, showed no abnormalities other than two well-healed abdominal scars. His heart was enlarged to 2 cm. beyond nipple line on left. Precordial bulge of the chest was apparent and a definite to-and-fro thrill was easily felt. The loud systolic and diastolic murmur was heard

best in the second left interspace, but was plainly audible throughout the area of cardiac dullness as well as in the neck and along the spine.

X-ray for the first time showed a prominence in the area of the pulmonic conus. Electrocardiogram showed no abnormality and almost no change since that of 1933.

Operation was done June 25, 1940. A ductus about 0.8 cm. in diameter and 0.8 cm. long was doubly ligated according to the technique of Gross under intratracheal ether. No difficulty was encountered and the patient stood it well.

Postoperatively his immediate course was excellent. June 30, he was out of bed, and walking on July 2, with the wound apparently healed. However, he began showing fever on July 3, and by July 5, it was apparent that an infection of the wound was present. The wound was opened on July 7, releasing several cubic centimeters of thick pus culturing *Staphylococcus aureus hemolyticus* from the subcutaneous tissue. The pleura was not involved and the temperature returned to normal but the wound continued to drain small amounts of pus.

On Aug. 9, 1940, the wound was opened widely under general anesthesia. One large pericostal silk suture and several silk knots were removed. No evidence of infection in cartilage or pleura was found. The wound was packed open and he was discharged on Aug. 17, 1940. Examination at this time showed no murmur and blood pressure of 96/64. X-ray of heart showed no abnormality of contour.

On Sept. 6, 1940, he was readmitted because of fever and cough. Examination showed numerous moist râles and rhonchi in the left chest, fewer on the right. His heart showed no change on physical examination and there was no evidence of pleural fluid. X-ray of the heart at this time showed a more prominent pulmonary arterial shadow than before operation, possibly due to relative diminution in size of the left ventricular shadow. He was discharged on Sept. 28, 1940, with his chest clear.

In the dressing clinic his wound had healed by Oct. 7, 1940, and he was discharged to a convalescent home.

On Dec. 3, 1940, he had gained nine pounds over his preoperative weight and eleven over his weight on discharge. He had had no cardiac symptoms and appeared in excellent health. His heart sounds were slow, strong, and regular, with an exaggerated P_2 but no murmurs.

On Feb. 3, 1941, he had gained eight more pounds and was eating well without urging. He had had only one cold lasting two days, in marked contrast to his previous winters. His heart sounds were unchanged.

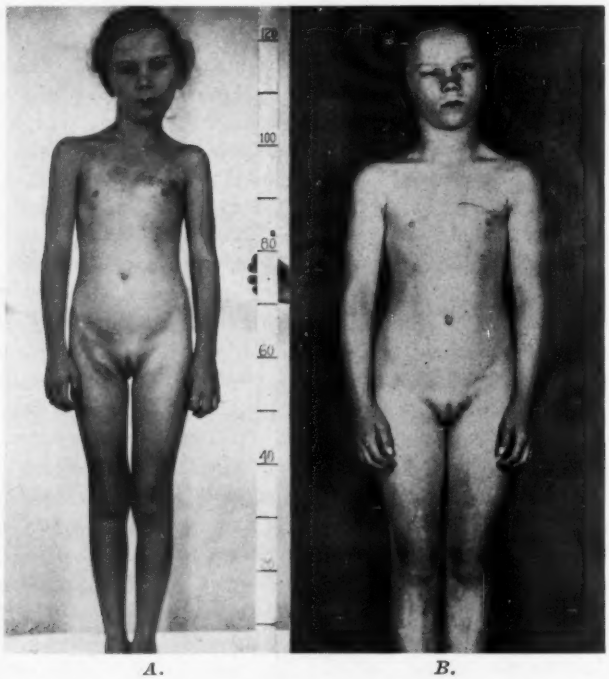
On June 6, 1941, he had continued in good health but had gained no more weight and had had another mild cold with cough. In August, 1941, he had another cold. However, his general vigor and health remained at a definitely higher level than before operation, he was eating well and beginning to develop sexually. His heart sounds remained free of murmurs.

CASE 4.—J. B. was born in the Swedish Hospital of Brooklyn in March, 1931, a breech delivery at full term. She was the second of three children of American parents. Both sisters and both parents are in good health and no familial diseases are known.

Her neonatal period passed uneventfully, feeding being by cow's milk formula with adequate vitamins added from the start. She was always rather small and thin but was not retarded in walking or talking. At no time did she have any spells of cyanosis. At 2 years of age her tonsils and adenoids were removed because of frequent colds. At three years, following a severe case of measles, a heart murmur was found to be present. This murmur was unassociated with any cardiac symptoms other than mild dyspnea and palpitation on exertion. She did not receive any treatment for her heart, nor was she restricted in activity at school, but she was always small and thin for her age and subject to frequent respiratory infections.

She was admitted to Babies Hospital on Sept. 9, 1940, for ligation of the patent ductus. Examination showed: Temperature, 99°; pulse, 90; blood pressure, 114/64; height, 4 feet 2 inches; weight, 50¾ pounds. She appeared puny but in good health and, aside from her heart, showed no abnormalities other than a right ptosis with asymmetry of the face and a tendency to hold the head off center without showing definite torticollis. Her heart was not enlarged and there was no precordial bulge. A mild thrill was present at the base, where a loud, harsh, crescendo systolic and diastolic murmur replaced the heart sounds. At the apex the sounds were of good quality and the murmurs could be heard only faintly in systole. The murmur was transmitted to the back and neck, but there was no "pistolshot" in the groin, no capillary pulsation in the nail beds, and no clubbing of the fingers.

X-rays of the chest showed a cardiac shadow which was normal in contour. Roentgenkymograph and fluoroscopy failed to show abnormal pulsations. Electrocardiogram was normal and electrostethogram showed a murmur characteristic of patent ductus.



A. *B.*

Fig. 4, Case 4.—*A*, One week after operation. The patient is small and thin but not markedly malnourished; torticollis is probably related to squint. *B*, Six months after operation. The gain in nutrition and vigor is obvious; not demonstrated is a considerable gain in height. Even the torticollis seems less conspicuous.

Operation was done Sept. 24, 1940. A small open ductus, about 0.8 cm. long and 0.4 cm. in outside diameter was found and ligated doubly according to the Gross technique, under endotracheal ether.

Postoperatively she did very well. On the first day her temperature reached 100°, thereafter remaining flat. She was up in a chair on the third day and walking on the sixth, when her stitches were removed, the wound being cleanly healed. The murmur heard preoperatively was completely absent on auscultation and on sound tracings taken on October 3. She was discharged on October 15, to a convalescent home.

On Nov. 18, 1940, she had gained eight pounds in the eight weeks since operation. She had no cardiac symptoms.

On Feb. 3, 1941, there had been no further gain in weight due to a recent respiratory infection, but she had grown in height and was able to exercise with much less fatigue than previously.

On May 5, 1941, she weighed 61 pounds and measured 51 inches, a gain of eleven pounds and two inches in the eight months since operation. She had been far more active than ever before and this activity had caused less fatigue than usual. She was aware that sensations of palpitation and discomfort previously present in her chest on exertion were absent. Heart sounds still showed a somewhat accentuated P_2 but no murmur.

CASE 5.—T. Y. was born at home on July 14, 1928, a normal full-term delivery. He was the fifth of nine children of American parents of German ancestry. A paternal aunt died in late adolescence due to congenital heart disease. Both parents and all eight siblings are in good health and no other familial disease is known.

He is said to have been a "blue baby" and to have remained more or less cyanotic for the first eight months of his life, after which cyanosis appeared intermittently in relation to exercise and also to cold damp weather. A loud cardiac murmur was recognized at birth. In spite of this he took artificial feedings well and developed at a normal rate. Respiratory infections were fairly frequent but never prolonged or severe. Exertion always caused dyspnea and he found it easier to breathe at night by elevating his head with two pillows. His shortness of breath caused him to tire rapidly and led to his placement in a special cardiac class at school. His weight and size were always less than his siblings at comparable age.

He was admitted to Babies Hospital on Dec. 30, 1940, for ligation of the patent ductus. Examination showed: Temperature, 99.6°; pulse, 88; respirations, 28; blood pressure, 130/45 with sounds still audible at zero; height, 4 feet 4 inches; weight, 57 pounds. He was a poorly developed little boy looking younger than 12 years of age, alert and cooperative and showing apparent pallor without cyanosis, but no evidence of acute illness. His fingers showed capillary pulsation in the nail beds, but no clubbing. His thorax was long and narrow with a definite though slight precordial bulge. His heart was enlarged to percussion. The apex impulse was clearly visible in the fifth interspace in the anterior axillary line and over the base a marked thrill was felt, most easily over the second left interspace where a long, loud, harsh systolic murmur was heard. This was transmitted throughout the cardiac area and into the neck and back. There was no diastolic murmur. Over the great vessels of the arms and legs a "pistolshot" systolic sound was present. The liver and spleen were not palpable and the remainder of the examination revealed no remarkable abnormalities.

X-rays showed a prominent pulmonary conus, enlargement of the heart to the left, and very marked increase in the caliber of the pulmonary vessels which showed conspicuous pulsation on fluoroscopy. Electrocardiogram showed no important findings and electrostethogram showed a long systolic murmur at the third left interspace and aortic area with short early diastolic murmurs, in addition, at the apex and pulmonic area.

Operation was done Jan. 9, 1941. A large ductus, about 2 cm. in diameter, was exposed and ligated with a single heavy silk ligature. The mediastinum appeared edematous and contained several large lymph nodes and dilated veins in the region of the ductus. Because of mediastinal bleeding a second ligature was not used, but bleeding was apparently controlled before closure. Intratracheal ether was used.

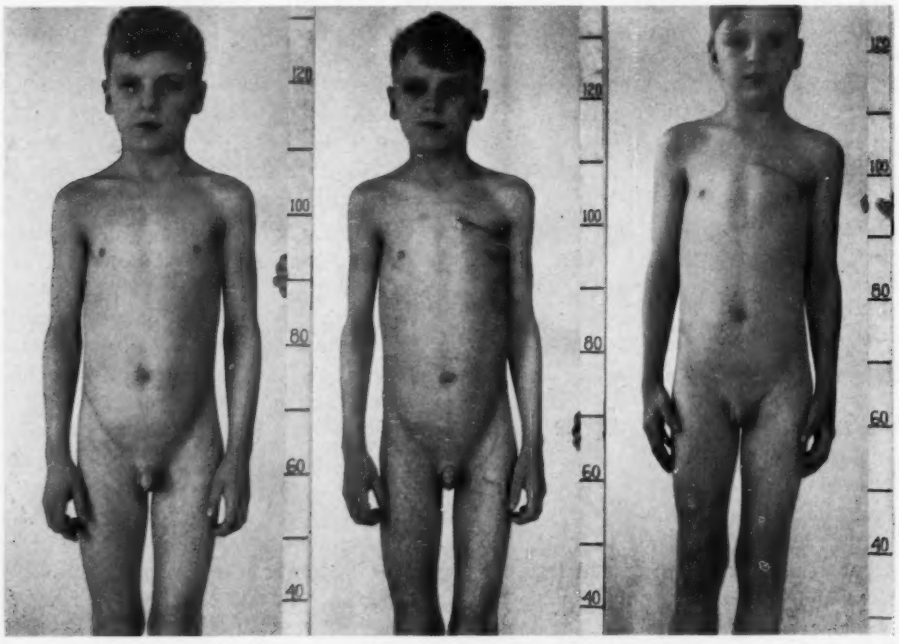
Postoperatively he became very restless and excited on recovery from anesthesia and in spite of a heavy sedative, thrashed about a great deal. He showed no respiratory distress for the first forty-eight hours, after which he developed dyspnea and evidence of fluid in the left chest. Thoracentesis at this time yielded 400 c.c. of bloody fluid. By the fifth day his temperature was normal but a severe epistaxis had resulted in pallor and prostration. The following day a murmur was found to

have reappeared, at first diastolic only but later more nearly continuous than before operation. In spite of this, his recovery continued without interruption. His wound was completely healed on the seventh day and he was allowed up on the ninth day. He was discharged on Jan. 23, 1941.

On February 3 he showed little change, his weight being the same as before operation and the nearly continuous murmur still present. X-rays of the chest showed some reduction in size of the superior mediastinal shadow and of the pulmonary conus, but still a grossly enlarged cardiac shadow.

On March 24, he still showed no striking improvement. He had had a fever of 103° the previous week, attributed to a sore throat. His chest signs were unchanged.

On April 28, the murmur seemed louder than before and for the first time since operation was accompanied by a thrill. He had been out of school for the preceding month because of fever attributed to respiratory infection.



A. *B.* *C.*

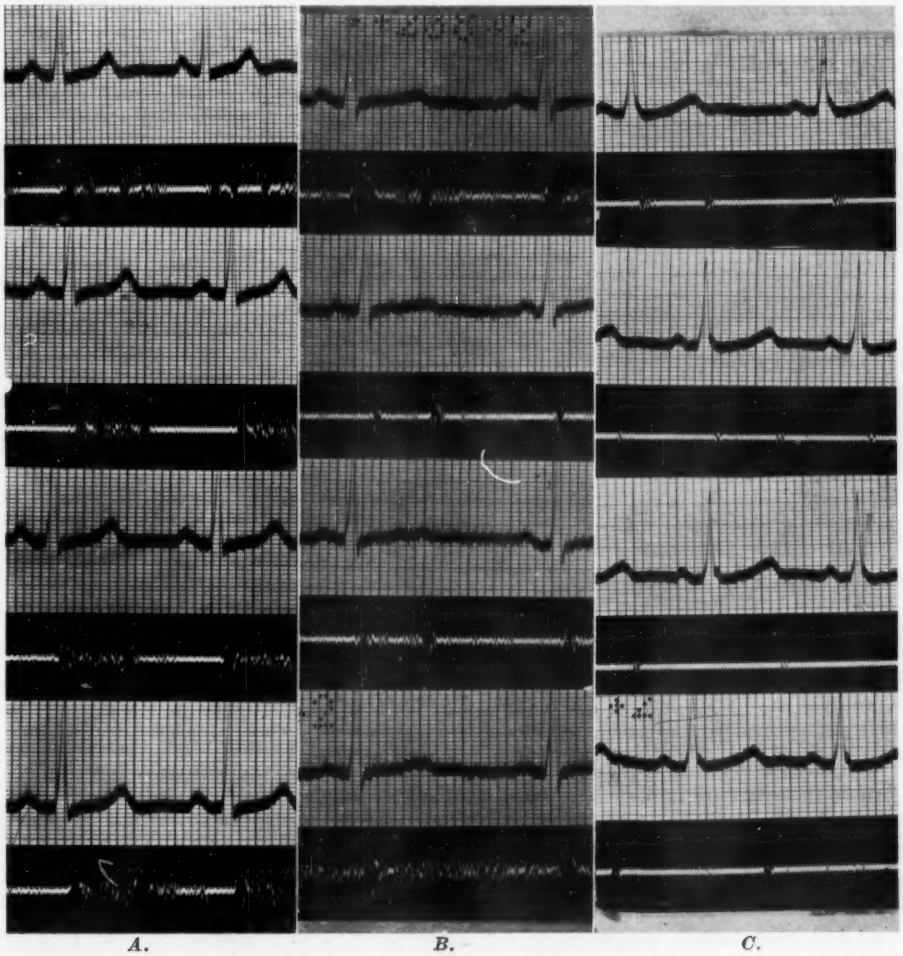
Fig. 5, Case 5.—*A*, Before operation. Nutrition is fairly good but the patient is very small and undeveloped for a boy of twelve years. *B*, Four months after the first operation. At this time the patency had recurred and he had had a positive blood culture for over a month. He is beginning to show emaciation. *C*, Two months after second operation. He is now better nourished and even a little taller than before the first operation. Improvement in these two months is conspicuous.

On May 6 he was readmitted to Babies Hospital for consideration of reoperation. Examination at this time showed: Temperature, 100.2°; pulse, 100; respirations, 36; blood pressure, 120/0; height, 4 feet 4 inches; weight 53 pounds. He was paler and thinner than on his first admission and somewhat dyspneic but still alert and cooperative. His heart was conspicuously enlarged with the point of maximum impulse in the anterior axillary line, sixth interspace. A precordial thrill was present after activity and absent at rest, but the pulmonary second sound could be palpated at all times. A loud, rough systolic murmur continuous with a softer diastolic was best heard under the well-healed scar over the second left interspace and was transmitted to the apex as well as to the back. Some tenderness and resistance was present over the liver, which could be felt two fingers below the costal

margin. The smooth, nontender spleen was readily felt four fingers below the costal margin. Capillary pulsation and "pistolshot" in the groin were again noted.

X-rays showed an enlarged heart with prominent pulmonary arterial shadow as well as conspicuous pulmonary bronchovascular shadows. The findings were less conspicuous than before operation. Electrocardiogram showed no significant changes. Electrostethogram showed a continuous murmur throughout the cardiac cycle.

Preoperatively he showed the presence of a hemolytic *Staph. aureus* on every blood culture. His fever varied up to 104.6° for the first week, during which sulfathiazole was given in increasing amounts. During the second week fever was lower with occasional spikes, while he was getting 4.5 Gm. of sulfathiazole a day. Because this resulted in a blood level of only 3 mg. per cent the dose was gradually increased to as much as 12 Gm. a day. By May 27, his blood contained 10 mg. per cent and his fever had disappeared, but the onset of toxic symptoms characterized by vomiting and severe leucopenia made it necessary to stop administration of the drug. Since organisms were still present in his blood, after a week without drug, sulfadiazine was begun. For the next three weeks, 6 Gm. a day were given, during which time his blood level varied from 6 to 10 mg. per cent. In spite of this,



A. *B.* *C.*

Fig. 6.—Stethograms of Case 5; apical, third left interspace, aortic arch, and pulmonic areas, from top to bottom. *A*, Before operation; systolic murmur at all stations with an early diastolic at the apex and pulmonic areas. *B*, One month after first operation; at all stations there are systolic and diastolic murmurs, being maximum in the pulmonic area. *C*, One month after second operation; the murmurs are no longer present.

organisms persisted in the blood stream and fever reappeared. On June 19, anti-staphylococcus immune rabbit serum,* 40 c.c. was given intravenously with an immediate temperature reaction to 105.6°, followed by a drop to 96° and a secondary rise to 104° within twelve hours. Throughout this preoperative period he had shown no petechiae or other peripheral embolic symptoms, but on frequent occasions complained of chest pain which was often accompanied by exacerbation of fever, and sometimes by transient pleural rubs. Cough and sputum were absent.

Reoperation was done June 24, 1941. The ductus was found wide open with a diameter of about 1.5 cm. and a considerably thicker wall than before. No trace of the heavy ligature was seen, though the former fine black silk ties were readily seen in the mediastinal scar. A double ligature of umbilical tape was used, with immediate elimination of the thrill, and 3 Gm. of sulfathiazole crystals were spread through the exposed mediastinal tissues.

Postoperatively his immediate reaction was good until twenty-four hours after operation, when his temperature reached 104° and he appeared prostrated. Dullness, bronchial breathing, and many fine râles developed over the left base and were considered to be due to atelectasis. On the second day sulfadiazine treatment was resumed and continued for seven days during which his chest signs slowly cleared, his temperature returned to normal, and his wound healed by primary union. A blood culture taken on the operating table grew hemolytic *Staph. aureus.* The first culture thereafter was taken on June 30, six days after operation; it failed to show growth. Four cultures taken during the following eight weeks were all sterile. On the tenth day, because sulfadiazine could not be obtained, the patient was given 2 Gm. of sulfathiazole. That evening his temperature suddenly rose to 104.4° and remained between 102° and 106° for three days, gradually falling to normal six days later. This was considered to be a drug reaction and no further medication was given. During the third, fourth, and fifth weeks after operation his temperature remained normal with occasional transient episodes of fever. His heart sounds were clear, without murmurs, his pulse quiet, and his diastolic pressure was maintained. His chest signs cleared entirely, though some density remained on x-ray and the shadow of his heart changed little. Electrocardiogram, which had shown an inversion of T_4F, returned to normal. Electrostethograms showed inconstant faint systolic murmurs which could not be verified on auscultation. Blood cultures remained negative. His activity increased slowly and he began to gain weight. By the sixth week he was walking, had gained eight pounds, no longer showed a palpable spleen, and seemed in excellent health. On August 22, he was discharged, fifty-nine days after operation, to a convalescent home.

On Oct. 20, 1941, his excellent health had been maintained. He had gained six more pounds and was able to return to school without disability. His heart sounds showed no murmur, his heart shadow by x-ray being smaller than at any time since first examined, but still showing a prominent pulmonary arterial bulge.

CASE 6.—R. H. was born at home on March 10, 1930, a normal full-term delivery. He was the second of three children of American parents. His older sister and younger brother are both in good health and show no congenital defects, and both parents are in good health. There is no history of cardiac disease or other familial illness in grandparents or parent's siblings.

His neonatal period was somewhat complicated by difficulty in feeding. Several formulas were used but he took them all poorly and gained only slowly. He had no cyanotic spells, but from earliest infancy a rapid and conspicuous cardiac pulsation had been noted which could also be seen in his neck. In spite of these difficulties he developed at a normal rate.

On May 11, 1934, he was first seen in Babies Hospital clinic because of a cold, cough, and fever of two weeks' duration. At this time examination showed a poorly

*Lederle Laboratories, Inc.

nourished child with a skull suggesting rickets, congested conjunctivae, inflamed pharynx, and thickened eardrums. There was a marked pulsation, visible in the neck, and a precordial pulsation visible beyond the nipple line, where a pronounced thrill could be felt. A loud rough systolic murmur was heard all over the precordium, greatest in the third left interspace, and the pulmonary second sound was increased. Blood pressure was 140/80. X-ray showed a markedly enlarged cardiac shadow, the outlines of which were confused by densities at both pulmonary hilae suggesting pulmonary congestion or tuberculosis. Tuberculin was negative.

During the next six years he was seen at the clinic at irregular intervals. He grew slowly and remained consistently underweight. He was subject to frequent respiratory infections, on one occasion had an epistaxis which required packing, and had bronchopneumonia at 5 years of age. An x-ray in 1937 showed cardiac enlargement and a prominent pulmonary arterial shadow, as well as exaggerated bronchovascular markings. Electrocardiogram showed slurred QRS complexes throughout. His diastolic pressure fell slowly as he grew but his murmur remained primarily systolic. He was very active, in spite of which he was placed in a cardiac class in school. During the winter of 1940 he contracted a severe bronchitis which kept him at home for long periods, during which time he failed to gain weight, so that his parents became willing to accept surgical intervention which had been suggested in the autumn.

He was admitted to Babies Hospital on May 5, 1941, for study, preparatory to ligation of the ductus. Examination showed: Temperature, 100°; pulse, 96; blood pressure, 116/40; height, 4 feet 5 inches; weight 55 pounds. He was a small, thin, overactive boy, very alert and cooperative. Aside from harsh breath sounds at the left base with occasional rhonchi, there were no significant abnormalities other than those related to the heart. There was no precordial bulge, but a marked visible and palpable systolic thrill was present over the entire precordium. The maximum apex impulse was felt in the anterior axillary line, sixth interspace, with the heart percussing correspondingly enlarged. A loud harsh systolic murmur heard with greatest intensity over the third left interspace was transmitted throughout the precordium, over the cervical vessels, and through to the back. An accompanying soft diastolic murmur was not transmitted. The pulmonic second sound was so loud it could be palpated. Though the pulse was of Corrigan type there was no true capillary pulsation or "pistolshot" in the groin. No clubbing or cyanosis was present.

X-rays showed all of the roentgen criteria necessary for a diagnosis of patent ductus arteriosus. They also demonstrated the presence of an anomalous hemivertebra in the thoracic spine. Electrocardiogram showed no important findings and electrostethogram confirmed the auscultatory findings.

Operation was done June 10, 1941. A thick-walled ductus 1.5 cm. in diameter was exposed and doubly ligated with woven cotton umbilical tape, under endotracheal ether.

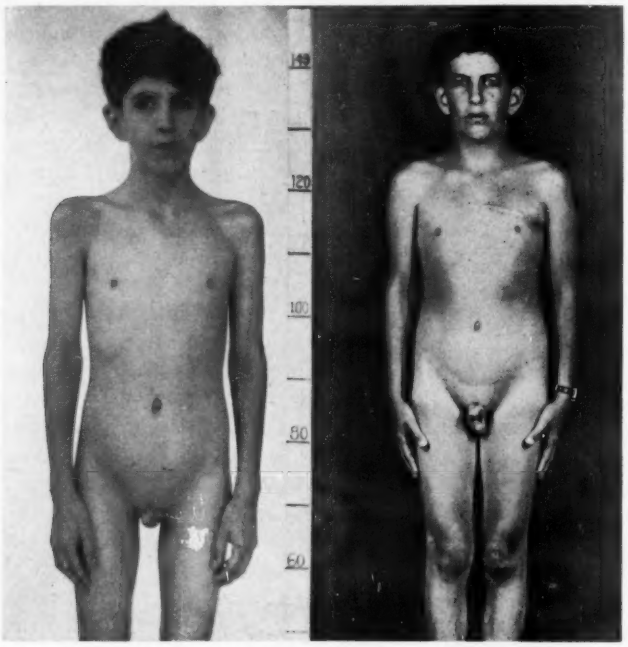
Postoperatively his temperature rose to 101° on the first day, subsiding to normal after the fourth. There were signs of patchy atelectasis over the left base which gradually cleared during the first week. He was allowed up on the seventh day at which time his sutures were removed, the wound being healed by primary union. At this time, though his pulse was slower and heart action quieter than before operation, a definite continuous murmur was again heard in the third left interspace, with transmission of the systolic element to the apex and aortic areas, but with no accompanying thrill. On the eleventh day he was discharged home.

On June 30 he had changed very little in the week since discharge, with the murmur conspicuously present but without accompanying thrill. He seemed in excellent condition, very active and alert, but had gained no weight. X-rays at this time showed no change in cardiac contour.

On Oct. 20, 1941, he had gained only four pounds in the four months since operation. His general condition appeared to have changed very little and he still showed

a conspicuous continuous murmur under the scar of his operation, the systolic element of which was transmitted to the base and aortic area. His blood pressure remained at 106/60.

CASE 7.—J. M. was born at the Summit Hospital on June 7, 1930, a normal full-term delivery. He was the oldest of three children of American parents. A brother drowned at 3 years of age, a sister six years old is living and well, as are both parents. As far as is known no other familial disease exists in the family of either parent.



A. *B.*

Fig. 7, Case 7.—*A*, Before operation. Poor nutrition is evident; at this time the patient had been running a positive blood culture for over a month. *B*, Two months after operation; marked improvement in nutrition and vigor is apparent.

His neonatal period passed uneventfully, with no retardation of development and normal growth on an adequate diet. When he was 13 months of age, a cardiac murmur was first noted, but there were no cyanotic spells or other evidence of disturbed function. His rate of growth and development were within normal limits, and it was not felt necessary to restrict his physical activity. It is probable, however, that exertion was more fatiguing to him than to his contemporaries, as he tended to avoid physical contests and became socially somewhat seclusive. He did not appear to be chronically ill, nor did he suffer from repeated respiratory infection. When he was 10 years old, because of faulty posture, spinal x-rays were taken which showed a faulty development of the bodies of most of the thoracic vertebrae, thought to be congenital in origin. Back exercises were prescribed.

On June 8, 1941, he complained of pain in both hips and the left knee, which showed some redness and swelling. He was found to have a fever of 103°, and three days later a typical measles rash appeared. The joint pains were transitory and trivial and the fever subsided to 101° after the appearance of the rash, but persisted intermittently after the rash had disappeared.

On June 28, 1941, he was admitted to Overlook Hospital because of continued fever, anorexia, and weakness. Two successive blood cultures at four day intervals grew *Streptococcus viridans*. Sulfathiazole by mouth was begun on July 4, 1941.

He was transferred to Babies Hospital on July 8, 1941, for consideration of further treatment. Examination showed: Temperature, 100.6°; pulse, 98; respirations, 30; blood pressure, 136/50; height, 4 feet 8½ inches; weight 71 pounds. He was a fairly well-developed and nourished boy of eleven, asthenic in habitus and round shouldered in posture, but not appearing acutely ill. There was slight pallor but no cyanosis and his skin was free of rash or petechiae. His thorax was thin and free of deformity other than a slight exaggeration of the spinal kyphosis. His heart was not enlarged; its pulsation was conspicuous, with maximum impulse on the fifth interspace, 6 cm. from the mid-sternal line; there was no definite thrill. A loud, systolic, swishing murmur was heard throughout the precordium but loudest in the third left interspace where a softer diastolic component was also present. The pulmonary second sound was accentuated. The systolic murmur was transmitted to the back, but there was no "pistolshot" in brachial or femoral arteries and no capillary pulsation in the nail beds. Liver and spleen were not palpable and no other abnormalities were noted.

X-rays showed a heart shadow within normal limits of size and shape except for a suggestive bulge in the region of the pulmonary conus. The lungs were clear and showed no conspicuous bronchovascular markings. Electrocardiogram showed only tachycardia, and electrostethogram showed systolic and diastolic murmurs in all leads.

Preoperatively he showed the presence of a *Strep. viridans* on seven successive cultures including one taken on the operating table. Sulfathiazole was continued at the rate of 3 Gm. a day for the first ten days. During this time his temperature showed daily swings to 102° and he became slightly cyanotic and nauseated. After a week without medication during which his fever did not change, he was given 500 c.c. of blood in two transfusions, and sulfapyridine was begun at the rate of 3 Gm. daily. This resulted in a good deal of nausea but during the following two weeks his fever gradually flattened to a daily rise to about 100°. During this time his blood contained 6 mg. per cent of sulfapyridine and continued to grow streptococci on culture.

Operation was done Aug. 8, 1941. A ductus about 0.9 cm. in diameter and 1.2 cm. long, with a fairly thin wall, was found. The surrounding mediastinum was somewhat edematous, and an enlarged lymph node which lay directly over the ductus showed Gram-positive cocci on smear. Two ligatures of umbilical tape were used to close the ductus. Sulfathiazole crystals, 3 Gm., were placed in the exposed mediastinal tissues.

Postoperatively he reacted very well. His temperature rose to 101° on the first day but reached normal on the second, where it remained. Sulfapyridine was given from the second to the seventh postoperative day, by which time his wound had healed by primary union. There was never any evidence of postoperative pneumothorax or atelectasis and no murmurs could be heard. A blood culture taken on the operating table grew *Strep. viridans.* The first culture thereafter was taken on August 11, three days after operation; it failed to show growth, as did one taken ten days, and a third, two weeks, after operation. On the seventh day he was allowed up and he began walking on the tenth. His appetite, vigor, and disposition improved dramatically during the second week. X-rays at this time showed little change in the cardiac shadow, electrocardiograms showed increase in amplitude of the T waves, and electrostethograms showed a persistent soft systolic murmur at the apex which could not be verified on auscultation. On August 28, twenty days after operation, he was discharged.

On September 29, he had gained eighteen pounds since before operation and was two inches taller than before his illness. His appetite for the first time was hearty, and he appeared and behaved more vigorous than before his acute illness. He had had no fever and no cardiac symptoms, and his heart sounds were strong, quiet, and free of murmurs.

On Oct. 22, 1941, he had gained four more pounds, was back at school carrying on with full activity. He had had no further fever and his cardiac signs were unchanged.

DISCUSSION

Sporadic attempts to ligate large blood vessels within the chest for the purpose of controlling hemorrhage have probably been made since the dawn of surgery. Such heroic efforts as Valentine Mott's,[1] over a century ago, even though successful in securing the vessel without opening the pleura, were doomed to failure because of infection. Undoubtedly this record contributed to the reluctance of surgeons to accept the suggestion made in 1907, by Munro,[2] even after aseptic surgery was well established, that a patent ductus arteriosus might be ligated. The first serious attempt was not reported until thirty years later when Graybiel and Strieder[3] recorded their failure due to hemorrhage in an adult with subacute bacterial endarteritis, an experience shared though not recorded by others. Gross's[4] success the following year resulted from his development of a new, deliberately transpleural, approach which enabled him to work out the technique of careful dissection[5] by which all subsequently reported ligations, including those reported here, have been done.

What, then, can be accomplished by this procedure? In a series of papers Gross and co-workers have recorded their experiences,[7, 8, 13] which they have summarized in a report of thirteen cases.[19] All of these cases were selected according to the indications worked out by Hubbard, Emerson, and Green.[6] One died, one, who has another vascular anomaly, has shown little change, and the remainder have shown gratifying and obvious improvement. Similarly, in the thirteen cases reported by Jones, Dolley, and Bullock,[10] with the exception of one fatality, the results were good though it is not clear in how many improvement was as conspicuous as in Gross's cases, or in those reported here. This may be due to the fact that these men have not been reluctant to urge operation on patients in whom the diagnosis was clear, but in whom general effects were not conspicuous, because of their conviction of poor prognosis due to ultimate blood stream infection.[9] Both Gross and Jones have carried out a considerable number of ligations since their last publications. Other ligations or attempts at ligation have also been reported recently by Miangolarra and Hull,[21] and still others have not yet been published.

It is clear that a patent ductus can be successfully obliterated by the method of Gross, and that this operation, carefully performed, is not one of great risk. If the mechanical effects of the presence of a patent ductus are as great as is indicated by the studies of Burwell, Eppinger, and Gross,[11, 14, 20] it would seem that an operation of comparatively little risk should be considered seriously in every case where the diagnosis is reasonably certain. On the other hand, their studies were carried out on Gross's patients, in whom the ductus was of such size as to cause definite clinical effects, and on animals in which a comparatively large shunt had been produced experimentally. There are many patients in whom

the diagnosis can be made, but who show little effect on their general health. It is uncertain whether the extra cardiac load is great enough in them to warrant the risks involved in eliminating it.

Both of the reported postoperative deaths were associated with infection, and the unsuccessful result of the first operation in Case 5 of this series was also associated with a complicating infection. Is the presence of infection in or near the ductus, then, a contraindication to operation? On the other hand, is the possibility of the eventual development of such infection a sufficient indication for operation even when the mechanical effects seem mild? This is the point of view held by Jones, Dolley, and Bullock. It is apparently supported by the fatal result in Streider's[3] case, and by the two fatalities reported by Touroff and Vesell.[16] On the other hand their first case,[15] though also a near fatality on the table, has remained free of disease over a year after recovery, and three subsequent cases, operated upon by the same surgeon, are also apparently cured.[17] Similarly, other cases ligated by Gross,[18] and by Bourne and his associates,[22] in the presence of subacute blood stream infection have remained free of infection postoperatively. In this series, the second operation on Case 5 and that on Case 7 seem to confirm the evidence that even an established subacute blood stream infection which has resisted intensive chemotherapy may be overcome by ligation of the duct.

Whether ligation of a patent ductus will prevent the formation of an infected thrombus near its site cannot be determined with certainty until a large number of ligated cases have been carefully followed for a long period. Though it seems reasonable to believe that infection may be prevented in this way, since the incidence of complicating infection is not certain, and since infection apparently may be overcome by prompt operation even after its occurrence, there is not yet sufficient evidence to warrant operation in every diagnosed case. For the present the operation is clearly indicated only if the patient shows evidence of mechanical overloading of the heart either by diminished cardiac reserve, by failure to grow and develop normally, by failure to maintain normal nutrition and resistance to infection, or if the ductus has become associated with an infected intimal thrombus with subacute blood stream infection.

SUMMARY

The results of eight instances of ligation of a patent ductus arteriosus in seven patients are reported. In six instances the ligation was carried out because of evidence of systemic effects of the mechanical circulatory abnormality. In two instances the ligation was carried out in order to overcome subacute bacterial blood stream infection which had resisted adequate chemotherapy with sulfonamide drugs.

No patient died following operation. In four instances the operation was conspicuously effective in overcoming the patient's mechanical circulatory symptoms. This improvement has been maintained for twenty-

eight, twenty-two, twenty, and seventeen months, respectively. In one instance the patency recurred, apparently due to cutting through of the ligature; this recurrent patency was subsequently ligated successfully. In one instance the result is uncertain. In the two cases in which infection was present at the time of operation, no subsequent blood culture has shown organisms, and the patients are conspicuously improved six and seven months after operation.

ADDENDUM.—In the year that has elapsed since this paper was written, all of the patients reported continue in good health except for R. H. (Case 6), reported previously as having a recurrent murmur and uncertain result. This boy died in June, 1942, of complications arising from the presence of a postoperative aneurysm of the ductus. Nine other patients have been operated upon without operative mortality. Five of these, aged 1, 3, 4, 7, and 18 years, were operated upon because of systemic symptoms. All have shown benefits varying from moderate to marked. Four were operated upon because of subacute blood stream infection. One, a woman of 30 years, has been free of infection for nine months; one, a woman of 24 years, died two months after operation of bacterial endocarditis due to an associated interventricular septal defect; one, a man of 42 years, is still living six months after operation with persistent murmur and persistent subacute blood stream infection; one, a girl of 12 years, is still in the postoperative period.

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AN EXPERIMENTAL STUDY OF SHOCK WITH SPECIAL REFERENCE TO ITS EFFECT ON THE CAPILLARY BED*

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THE loss of circulating fluid with the corresponding decrease of volume of blood has long been known to be an important factor in the condition of secondary shock. Interest has centered on the capillary bed as a site where the fluid is lost. In this study the hepatic and mesenteric capillaries of the rat, under normal conditions, were compared with the capillaries of animals in which traumatic shock had been produced experimentally by different means in an attempt to obtain more exact knowledge of the capillaries in shock than may be observed by microscopic examination of fixed specimens. An occlusive circulatory type of shock, similar to that used previously by Allen, and more recently by Selye and Dosne, was used not only to study capillary changes but also to determine the efficacy of different methods for restoring the circulating fluid.

A comprehensive review of the literature concerning shock is unnecessary since the pertinent investigations on the subject have been presented by Cannon, Boyers, Moon, O'Shaugnessy and Slome, Blalock, and Harkins.

APPARATUS USED AND METHODS OF STUDY

A modification of the method of transillumination described by Knisely was used throughout this study and made possible the direct observation of the capillaries by means of transmitted light.§ The light source was a 400 watt bulb. The light was transmitted through a rod, which was leucite at the proximal end and silvered quartz at the distal end, and passed through an aperture measuring 2 by 3 mm. The tissue of the animal to be examined was placed over the end of the rod and direct microscopic examination of individual capillaries was made. Precautions were taken constantly against cooling or drying of the tissues. Thus, the platform on which the animal was placed was kept at body temperature, warm Ringer's solution was kept continously flowing from the end of the rod beneath the tissues being examined, and Ringer's solution was passed over the top of the organ being examined.

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Six-week-old albino male rats of the Wistar strain, ranging from 70 to 140 Gm. were used. Pentobarbital sodium (nembutal) was used throughout as an anesthetic agent in subcutaneous doses of 30 mg. per kilogram. As necessary, 1 to 1.5 mg. more was given. No effect on the capillaries from such doses was ever noted.

The normal circulation of the mesentery and liver was studied first. A routine of using one area of the mesentery only once for observation was adopted. Observations were made first on the mesenteric field at the ileocecal junction and further observations during the course of the experiment were made on successive fields passing proximally. As far as was possible, a similar routine was adopted for study of the borders of the liver, beginning at the far left border and observing successive fields to the right. These various fields were studied with the binocular stageless microscope using 40, 150, and, by use of a water immersion lens system, 600 magnifications.

The effects of local and intravenous administration of histamine were observed on both the mesenteric and hepatic circulation.

A condition simulating shock was not produced by simple laparotomy, exposure of the intestines, or crushing trauma to the limbs. A shock-like condition was produced by any of the following three methods:

1. Intestinal manipulation: The intestines were manipulated firmly but gently, so that no gross hemorrhage occurred. The manipulation was continuous for five minutes. The intestines then were left exposed on the warm platform for the remainder of the period of observation.

2. Exposure of intestines to cold: The animal was placed on a glass plate, which in turn was placed on a piece of ice. The intestines were removed from the abdominal cavity and spread over the glass plate.

3. Application of rubber bands to thighs: The animals were given pentobarbital sodium and rubber bands were tied tightly, high on the legs. The animals then were left alone for five to five and one-half hours. At this time the animals were again given pentobarbital sodium and the abdomen was opened. After observations of the capillaries of mesentery and liver had been made, the rubber bands were cut.

In all types of shock, observations of respiration and of mesenteric and hepatic capillaries were made and recorded every fifteen to thirty minutes. After the findings in these different types of shock had been confirmed on numerous occasions, further studies were made in an attempt to correlate the state of shock with the concentration of blood. Erythrocyte counts and hematocrit readings (Van Allen method) were made on the blood secured by means of cardiac puncture three days to one week before shock was induced experimentally. Specimens of blood were obtained again just before death in the condition of shock.

RESULTS

1. The Normal Animal

Observation of the mesenteric circulation reveals, with all magnifications, a glistening white background which is composed of the fat

cells. Only occasionally a few small functioning capillaries (12 to 14 μ) containing a very rapid blood flow are seen among these fat cells in the normal animal. The larger capillaries (20 to 40 μ) are often seen but the circulation is so rapid within them that the individual cells cannot be delineated. The largest capillaries (150 to 250 μ), which connect the main arteriole and venule, stand out the most distinctly but the circulation within these vessels is even more rapid. The main arterioles and venules (400 to 500 μ) have such a rapid circulation that movement cannot be recognized.

Thus, as the mesentery is examined with the usual 150 magnification the main observations are indistinctness of the capillaries, the glistening white background, and the extreme rapidity of the circulation. Within the course of one to two hours, a few newly functioning capillaries appear and there is a slight slowing of the speed of the circulation. This final condition of the capillaries persists for six to seven hours and if at the end of that time the abdominal wound is repaired, the animal appears to be normal the next day.

The circulation within the liver is studied most satisfactorily with the 600 magnification water immersion system. With this magnification the appearance of the sinusoids (40 to 50 μ) is variable not only in their content but also in the speed of the blood flowing through them. When first examined, many of the hepatic sinusoids are empty, a few contain cells but are inactive, and others reveal such a rapid circulation that the individual cells cannot be recognized. The circulation within the larger vessels is extremely rapid. Gradually during the following eight hours, there is a slowing of the sinusoidal circulation, making it possible to observe individual cells in the rapidly moving current. It is unusual for an alteration of the circulation in the large vessels to occur. At the end of this eight-hour period, there are fewer sinusoids in the inactive phase and all the sinusoids are more congested than at the beginning of the examination but there is no sluggishness of circulation or generalized stasis.

2. Effect After Administration of Histamine

There was no change in the appearance of the capillaries of the mesentery or liver following the local application of a 1 per cent solution of histamine.

Variable effects, depending on the dose, were observed after intravenous administration of histamine. Any effect after intravenous administration of 1 to 6 mg. of histamine was rarely noted. However, there was observed the appearance of newly functioning capillaries in the mesentery with some slowing of the flow of blood with doses of 6 to 12 mg. of the histamine base. Nothing definite was noted in the liver with such doses. Very definite results occurred when 12 to 20 mg. of the base per 100 Gm. of body weight was given. Many newly functioning capillaries appeared, the larger capillaries stood out more distinctly, there was a definite slowing of the circulation, and congestion and

dilatation occurred. The sinusoids of the liver were congested and the flow of blood was slowed in both the sinusoids and larger vessels. The mesenteric circulation gradually returned to normal within ten to fifteen minutes, the hepatic circulation returning to normal in ten to thirty minutes. The lethal dose was found to be 27 to 33 mg. of histamine base for a rat weighing 100 Gm.

The main feature accompanying the capillary change was a marked decrease in respiration, from a range of 80 to 100 to a range of 60 to 70 respirations a minute. Also coinciding with the return of the capillaries to normal, the respirations would become normal again within ten to fifteen minutes after the intravenous injection of histamine.

When the lethal doses were administered the respirations decreased quickly, the capillary changes were minimal, and often no difference was observed from the normal except for the cessation of flow of blood.

Lacrimation; profuse, watery mucoid discharge from the nose and mouth; restlessness; increased peristalsis; occasional convulsive seizures of the limbs, and also, on occasions, micturition and defecation occurred with doses of 8 to 20 mg. of histamine administered intravenously.

3. Experiments Dealing With Shock

a. Intestinal Manipulation (Table I).—*(1) Mesentery:* A pink background developed, replacing the normal glistening white background within fifteen to thirty minutes after the intestinal manipulation. This

TABLE I

EFFECT OF INTESTINAL MANIPULATION FOR FIVE MINUTES

NUMBER	WEIGHT (GM.)	DURATION OF LIFE	DIFFERENCE IN RED BLOOD CELLS*	DIFFERENCE IN HEMATOCRIT (PER CENT)	CAPILLARY RESPONSE
			MANIPULATION		
1	101.5	1°40′	3.31	19	Mesentery: A pink background developed within 15 to 30 minutes, and within 30 to 60 minutes hemorrhages appeared in many fields
2	105.0	25′	0.74	5	
3	99.8	2°19′	1.81	8	
4	82.4	21′	0.30	6	
5	82.8	46′	2.29	19	Liver: Sluggish circulation developed in all the sinusoids within 15 to 30 minutes with gradual stasis occurring
			CONTROLS		
1	57.2	2°30′+	0.04	1	Mesentery: Capillaries not clearly delineated, white background, rapid circulation; after 30 to 60 minutes, new small capillaries appeared, but circulation remained rapid
2	86.8	1°20′+	−0.64	0	Liver: More sinusoids gradually resumed activity but circulation remained very rapid throughout

*Millions per c. mm. of blood.

change was due to the appearance of newly functioning capillaries which were congested and stasis rapidly developed. Dilatation and congestion occurred in the larger capillaries and the circulation became sluggish. Groups of red blood cells appeared in many fields outside of the capillaries in thirty minutes to one hour.

(2) Liver: All the sinusoids became active; however, the circulation was sluggish within fifteen to thirty minutes after the intestines had been manipulated and gradual stasis took place. Even though there was increased sinusoidal activity, congestion was not as marked as is often seen in the normal liver.

After the capillary response in this type of shock was established, hematocrit and red blood cell studies were done and often the values were found to be quite variable. The respirations remained at 80 to 90 a minute; however, a few minutes prior to death they would gradually decrease, become gasping, and finally cease.

b. Exposure of Intestines on Iced Plate (Table 2).—

(1) Mesentery: The circulation usually remained very rapid throughout this type of shock, even though the respiration would cease temporarily for ten to fifteen minutes. A few newly functioning capillaries appeared but stasis did not occur until shortly before the death of the animal and dilatation with congestion usually was not seen.

TABLE II

EFFECT OF EXPOSURE OF INTESTINE ON ICED PLATE

NUMBER	WEIGHT (GM.)	DURATION OF LIFE	DIFFERENCE IN		CAPILLARY RESPONSE
			RED BLOOD CELLS*	HEMATOCRIT (PER CENT)	
			EXPOSURE		
1	87.2	1°40′	−0.52	−5	Mesentery: Even though respirations stopped for 10 to 15 minutes, circulation remained very rapid; new capillaries appeared but stasis was terminal Liver: Sinusoids active and congested; often seen were groups of red blood cells outside the sinusoids
2	96.0	1°40′	0.50	3	
3	98.0	1°45′	1.42	17	
4	66.2	48′	−0.25	−8	
			CONTROLS		
1	104.4	1°40′+	−0.59	−6	Mesentery and liver: As in normal control in Table I
2	102.8	2° +	0.37	−1	

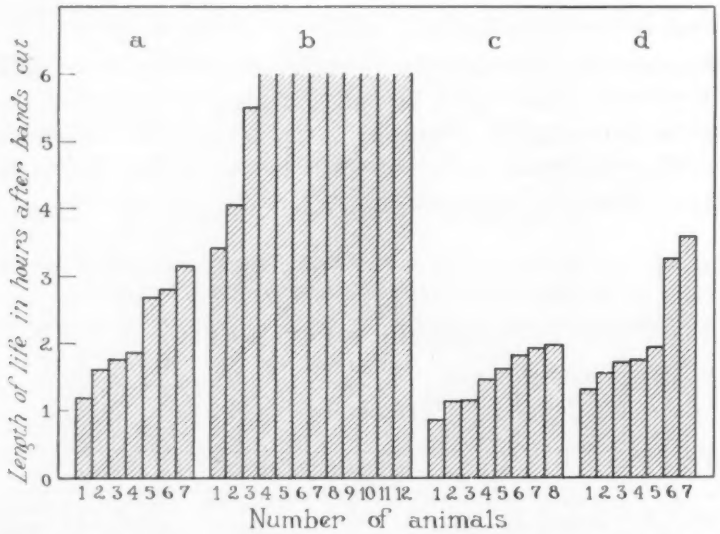
*Millions per c. mm. of blood.

(2) Liver: The sinusoids became very active and congested and groups of red blood cells often were seen outside of the sinusoids. Gradual slowing took place thirty to forty-five minutes prior to death and stasis finally occurred. More congestion of the sinusoids was seen in this type of shock than in any other type.

The animal was placed on a glass plate over ice with the intestines spread out on the plate. The respirations would decrease and become

irregular within eight to twelve minutes, and ten to twenty minutes later the respirations would cease entirely. The animals were left in such a condition as long as twenty minutes without being disturbed. Finally when they were examined, the foregoing capillary changes were observed. The rats then were placed on the warm platform. After the animals had been on the warm platform for two to three minutes, the respirations gradually began to increase but did not return to the normal rate. This sequence of events would repeat itself; each time that the rat was placed on the warm platform the respiratory rate would increase but each time the maximal respiratory rate was less than on the previous occasion. Finally, the respirations ceased entirely even when the animal was kept on the warm platform.

There was no consistency in the results of hematocrit and red blood cell studies in this type of shock.



Figs. 1 to 4 show the same relationship, that is, the ordinate is equal to the number of hours that the animal lived after the rubber bands were cut and the abscissa represents the number of animals used in each series.

Fig. 1.—Study of the causation of the rubber band type of shock. *a*, The usual rubber band type of shock; *b*, the legs of the animals were wrapped tightly before the bands were cut; *c*, the wrappings were removed from the legs one hour after the bands were cut; *d*, spinal cords resected before the bands were cut.

c. Application of Rubber Bands to Thighs (Table III, Fig. 1, *a*).—

(1) Mesentery: There was no change from the normal capillary circulation either before the bands were cut or for thirty to sixty minutes after the cutting of the bands. At this time, newly functioning capillaries appeared and there was a slowing of the speed of the circulation. The larger capillaries stood out more distinctly than before and dilatation occurred. Gradually the circulation became sluggish and stasis resulted shortly before the death of the animal.

(2) Liver: The circulation remained normal for thirty to ninety minutes after the rubber bands were cut. All the sinusoids gradually

TABLE III

EFFECT OF RUBBER BANDS ON THIGHS FOR FIVE TO FIVE AND ONE-HALF HOURS

NUMBER	WEIGHT (GM.)	DURATION OF LIFE	DIFFERENCE IN RED BLOOD CELLS*	DIFFERENCE IN HEMATOCRIT (PER CENT)	CAPILLARY RESPONSE
RUBBER BANDS ON THIGHS					
1†	76.5	0	0.32	−2	Mesentery: Entirely normal for first 30 to 60 minutes after bands had been cut; then new capillaries appeared, main capillaries stood out more clearly, circulation slowed and became sluggish as capillaries became dilated, congested and finally static Liver: Remained normal for 30 to 90 minutes, then gradually the circulation became sluggish and stasis occurred first in sinusoids, then in larger veins; often not as much congestion as normal
2	101.6	2°46′	1.73	16	
3	104.5	3°9′	3.33	19	
4	110.5	2°40′	2.64	21	
5	67.0	1°53′	1.73	19	
6	78.4	1°12′	3.34	34	
7	100.5	1°37′	4.76	40	
8	107.7	1°45′	3.54	28	
CONTROLS					
1	94.0	2°37′	0.45	−7	Mesentery and liver: As in normal control in Table I
2	85.4	1°55′+	−0.78	−8	
3	101.0	2°5′+	1.10	−1	

*Millions per c. mm. of blood.
†Died from effect of pentobarbital sodium before bands were cut.

became active but often they were not as congested as they are normally. The circulation became sluggish and finally stasis occurred, first in the sinusoids and then in the larger veins.

Edema rapidly accumulated in the legs of the animals after the bands were cut, being so marked that the legs became abducted and externally rotated. The average increase of the circumference at the tibial tubercle from the time that the bands were cut until the respirations had ceased was 0.7 to 0.8 cm.

4. Studies in Regard to Causation of the Rubber Band Type of Shock

a. Wrapping of the Legs (Table IV, Fig. 1, *b*).—The legs of the animals were wrapped tightly with waterproof adhesive tape just before the bands were cut. These wrappings were reinforced further with tape after the bands were cut.

(1) Mesentery and Liver: The usual capillary response was that of the normal control animal. Unless the legs were wrapped tightly, some edema did develop under the tape and the usual capillary response to shock was present, hemoconcentration occurred, and the animals died.

The controls in this series were divided into two groups. Group *a* consisted of animals whose legs were wrapped tightly with tape at the same time the other animals' legs were wrapped, but no rubber bands had been applied previously.

Group *b* consisted of animals whose legs were wrapped tightly with tape for five hours and then the tape was removed.

TABLE IV

EFFECT OF RUBBER BANDS ON THIGHS AND WRAPPING OF LEGS WHEN BANDS WERE CUT

NUMBER	WEIGHT (GM.)	DURATION OF LIFE	DIFFERENCE IN		CAPILLARY RESPONSE
			RED BLOOD CELLS*	HEMATOCRIT (PER CENT)	
			LEGS WRAPPED TIGHTLY		
1	93.4	4°2′	0.82	4	Mesentery: Usually the normal capillary circulation was seen throughout the entire six-hour period
2	94.0	6°+	0.27	4	
3	106.0	6°+	0.52	1	
4	104.0	6°+	0.05	−3	Liver: Not different from normal, sinusoids remaining very active throughout
5	118.4	6°+	0.48	1	
6	121.1	3°25′	0.82	17	
7	124.8	6°+	0.87	3	Note: Only abnormal feature seen in this group was the edema of the scrotum and penis, with occasional urethral discharge. This edema was very marked in Animal 6 and the scrotum became enormous and blue; this was the only animal in the group which had the usual capillary changes seen in shock (see Table III)
8	87.0	5°29′	0.30	8	
9	112.5	6°+	0.07	−2	
10	106.0	6°+	0.44	6	
11	130.6	6°+	0.06	−2	
12	126.4	6°+	0.14	1	
			LEGS WRAPPED LOOSELY		
1	106.0	3°9′	1.21	25	Mesentery and liver: Capillary changes as seen in Table III
2	100.2	2°50′	0.43	14	
			CONTROLS A: ONLY LEGS WRAPPED; RUBBER BANDS NOT APPLIED		
1	89.2	2°46′	0.49	8	Mesentery and liver: Entirely normal (Table I)
2	104.1	3°12′+	0.27	4	
3	92.4	6°+	−0.80	−4	
4	137.2	6°+	0.54	8	
			CONTROLS B: LEGS WRAPPED THEN TAPE REMOVED		
1	128.2	6°+	0.35	3	Mesentery and liver: See normal control in Table I; even though these legs were wrapped very tightly, the tourniquet effect of the rubber band was not present
2	126.4	6°+	0.30	−4	
3	128.6	6°+	0.07	−1	

*Millions per c. mm. of blood.

An experiment then was done to observe the effects of temporary splinting of the legs (Table V, Fig. 1 *c*). The rubber bands were placed around the hind legs for the usual five-hour period, the legs were wrapped tightly with adhesive tape, and the bands were cut. At the end of one hour the adhesive tape wrappings were removed. The legs began to swell rapidly and within thirty minutes the usual capillary response seen in the rubber band type of shock developed. Hemoconcentration was present and there was the usual increase of the size of the legs. The controls in this group were animals on whose legs the rubber bands were left throughout the entire experiment and all of these animals lived for the six-hour period of observation. The capillary response was that of the normal animal; there was no increase of the size of the legs and hemoconcentration did not develop.

TABLE V

EFFECT OF REMOVING WRAPPING OF LEGS AN HOUR AFTER RUBBER BANDS WERE CUT

NUMBER	WEIGHT (GM.)	DURATION OF LIFE	DIFFERENCE IN RED BLOOD CELLS*	DIFFERENCE IN HEMATOCRIT (PER CENT)	CAPILLARY RESPONSE
LEGS WRAPPED TIGHTLY WHEN BANDS WERE CUT; TAPES OFF AFTER 1 HOUR					
1	123.4	53′	1.92	21	Mesentery: Entirely normal until 15 to 30 minutes after removal of wrappings, then the usual change of appearance of new capillaries, slowing circulation, increasing congestion, sluggishness, dilation, and terminal stasis was seen
2	127.2	1°37′	1.98	23	
3	124.2	1°8′	2.07	29	
4	168.2	1°9′	2.37	36	
5	163.2	1°28′	2.40	25	
6	155.4	1°48′	2.45	30	
7	139.2	1°57′	1.06	19	
8	110.0	1°54′	2.96	28	Liver: No change from normal until after removal of wrappings; then gradual slowing of the circulation in the sinusoids with stasis and finally stasis in the larger veins of the liver were seen
CONTROLS: BANDS LEFT ON					
1	102.6	6°+	0.26	− 3	Mesentery and liver: No difference from the normal control animals of Table I
2	103.4	6°+	0.15	6	
3	125.2	6°+	−0.45	−10	
4	140.4	6°+	−0.99	0	

*Millions per c. mm. of blood.

The question then arose: When the legs are wrapped tightly with adhesive tape, is not the same tourniquet effect present as though the rubber bands were left on throughout the experiment? The adhesive wrappings were proved not to have such an effect by the following observations:

1. When the bands were cut, even though the legs were wrapped tightly, there was a return of the feet to a more normal color.

2. Small cuts and bites on the feet would bleed when the bands were cut, even though the legs were wrapped tightly.

3. Shock could not be produced (control Group *b*, Table IV) by wrapping the legs tightly for five hours and then removing the wrappings.

In order to determine whether the rubber band type of trauma was caused by bombardment of sensory impulses from the traumatized region, the lumbar portions of the spinal cords of eight rats were sectioned. The length of life of seven of the rats after the rubber bands were cut is given in Fig. 1, *d*. Further details are presented in later paragraphs.

In order to check further the effect of preventing loss of fluid by wrapping the legs, two dozen animals were divided into four groups.

Group *a* was composed of six animals with rubber bands placed around all four legs for more than four hours. The bands then were cut. No animal lived longer than two hours and thirty-two minutes (Fig. 2, *a*).

Group *b* was composed of the same number of animals and the same method was used, except that all four legs of the animals were wrapped

TABLE VI

EFFECT OF SECTION OF THE SPINAL CORD ON RATS WHOSE LEGS WERE CONSTRICTED WITH RUBBER BANDS

TIME CORDS CUT	NUMBER	WEIGHT (G.M.)	DURATION OF LIFE	DIFFERENCE IN RED BLOOD CELLS*	DIFFERENCE IN HEMATOCRIT (PER CENT)	CAPILLARY RESPONSE
When bands were cut	1	138.0	1°18′	3.25	25	Mesentery and liver: First four animals as described in Table III, the typical gradual onset of capillary stasis
	2	99.4	1°41′	3.03	24	
Five hours before bands were cut	3	129.2	----	−0.61	− 2	However, in Animals 5 and 6 and to a greater degree in Animals 7 and 8 there were multiple new capillaries in the mesenteric field on first examination with slower circulation than normal; this was not seen in the hepatic sinusoids
	4	104.6	1°44′	1.99	23	
Two days before bands were applied	5	113.0	1°33′	1.69	17	
	6	127.6	3°34′	3.01	21	
Four days before bands were applied	7	144.8	1°57′	2.63	18	
	8	144.6	3°17′	2.39	24	
CONTROLS						
When bands were cut	1	134.8	3°+	0.70	5	Mesentery and liver: Same as normal with exception of Animal 3 which revealed the multiple new capillaries in the mesentery and no change after 4 hours
Five hours before bands cut	2	141.6	2°+	0.55	1	
Two days before bands applied	3	140.6	4°+	0.02	− 5	

*Millions per c. mm. of blood.

TABLE VII

EFFECT OF INTRAVENOUS INJECTION OF RINGER'S SOLUTION WHEN RUBBER BANDS WERE CUT

NUMBER	WEIGHT (GM.)	DURATION OF LIFE	DIFFERENCE IN RED BLOOD CELLS*	DIFFERENCE IN HEMATOCRIT (PER CENT)	CAPILLARY RESPONSE
1	129.4	3°16′	1.35	17	Mesentery: Following intravenous injection many new capillaries became apparent, with slight slowing of circulation; one hour later, usual changes seen in shock developed. Liver: Not different from the capillary effects described in Table III.
2	92.0	2°33′	2.55	30	
3	130.5	3°9′	1.57	18	

*Millions per c. mm. of blood.

tightly with adhesive tape just before the bands were cut. Two of these animals lived for six hours but were dead at the end of twenty-four hours (Fig. 2, *b*).

Rubber bands were applied to the hind legs of Group *c* for five and one-half hours and then cut. The longest period of life was four hours and forty-seven minutes (Fig. 2, *c*).

Rubber bands were applied to the hind legs of Group *d* and the legs were wrapped tightly with adhesive tape before the bands were cut. All six of these animals lived throughout the six-hour period of observation, five lived for twenty-four hours and three were living at the end of five days (Fig. 2, *d*).

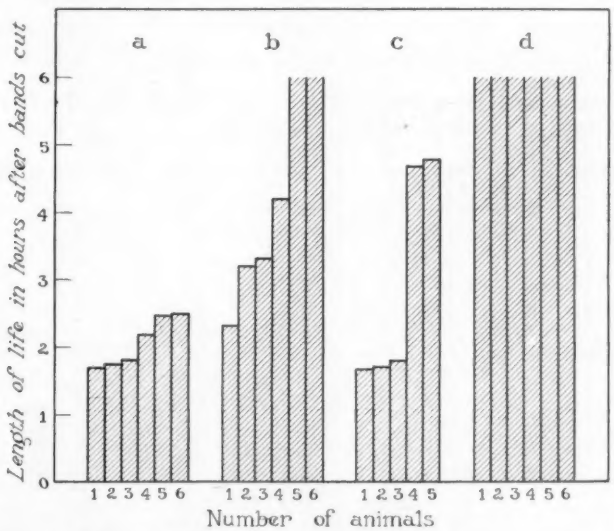


Fig. 2.—Further study, showing the importance of local loss of fluid. *a*, Bands placed around all four legs and then cut; *b*, bands placed around all four legs, then legs wrapped tightly before the bands were cut; *c*, bands placed around hind legs and then cut; *d*, hind legs wrapped tightly before bands were cut.

b. Section of the Spinal Cord (Table VI, Fig. 1, *d*).—The lumbar portion of the spinal cord was sectioned and the distal segment of the cord was needled. In some of the animals, $^{15}/_{100}$ c.c. of 10 per cent procaine hydrochloride was injected into the distal segments of the spinal cords.

(1) Mesentery: Animals whose spinal cords had been sectioned either just before or just after the rubber bands were cut revealed the usual changes seen in the rubber band type of shock. However, in the other animals in this group, whose spinal cords had been sectioned two to four days before the rubber bands were applied, there were innumerable newly functioning capillaries. Congestion and dilatation were generalized and the circulation was much slower than normal. The only noticeable change after the bands were cut was a gradual slowing of the circulation, occurring forty-five minutes or later with terminal stasis. Cord bladders were also very prominent in this latter group.

5. Intravenous Therapy With the Rubber Band Type of Shock

a. Ringer's Solution (Table VII).—Ringer's solution, 3 c.c. was given intravenously into the inferior vena cava over the course of one minute at the time the rubber bands were cut.

(1) Mesentery: Following the intravenous injection, newly functioning capillaries appeared and the circulation was slower than normal, but no obvious dilatation or congestion was present. About one and one-half hour later, the circulation became much slower and dilatation and congestion occurred with terminal stasis.

(2) Liver: Following the injection, all of the sinusoids became active but not congested. After one and one-half hour, the circulation gradually slowed down and terminal stasis occurred.

On comparison of untreated rats to the thighs of which rubber bands had been applied (Fig. 3, *a*) with the rats that had received Ringer's solution (Fig. 3, *b*), it was evident that life was prolonged to some

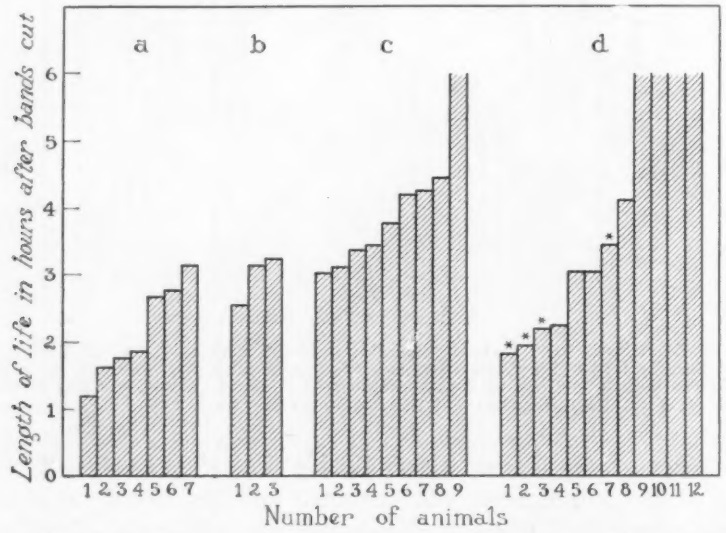


Fig. 3.—Effects of intravenous therapy. *a*, Usual rubber band type of shock in untreated rats; *b*, Ringer's solution given intravenously before bands were cut; *c*, whole blood given intravenously before bands were cut; *d*, blood plasma given intravenously before bands were cut.

*Denotes that hemorrhage occurred.

extent in the latter group and it was necessary to give an additional dose of pentobarbital sodium to each animal in this series; whereas, with the usual untreated type of rubber band trauma, none but the initial dose of pentobarbital sodium was needed.

The legs were much more edematous than in the ordinary type of rubber band trauma and hemoconcentration was present.

b. Whole Blood (Table VIII).—Rat's whole blood, 15 c.c., was mixed with 2 c.c. of a 2.5 per cent solution of sodium citrate. This mixture was filtered through gauze and 3 to 4 c.c. was given intravenously at the time the rubber bands were cut.

(1) Mesentery: Many newly functioning capillaries appeared and marked congestion developed with slowing of the circulation. In all cases, stasis occurred about one to two hours before the respirations ceased.

TABLE VIII

EFFECT OF INTRAVENOUS INJECTION OF WHOLE BLOOD WHEN RUBBER BANDS WERE CUT

NUMBER	WEIGHT (GM.)	DURATION OF LIFE	DIFFERENCE IN		CAPILLARY RESPONSE
			RED BLOOD CELLS*	HEMATOCRIT (PER CENT)	
1	97.5	3°2′	4.99	30	Mesentery: Following intravenous injection, many new capillaries appeared, with congestion and slowed circulation. The capillaries of Animal 7 remained this way; the other animals gradually went into shock, however, capillary stasis was present 1 to 2 hours before death rather than being a terminal phenomenon. Liver: Sinusoids were very full and distended, after intravenous injection and stasis occurred 45 minutes to 1½ hour before death
2	122.2	3°47′	3.62	21	
3	120.6	4°17′	3.46	29	
4	109.7	4°26′	4.92	36	
5	127.2	4°12′	3.91	29	
6	116.0	3°27′	3.64	31	
7	130.6	6°+	0.71	16	
8	112.5	3°23′	3.07	37	
9	130.4	3°7′	2.03	19	

*Millions per c. mm. of blood.

(2) Liver: Increased activity of the sinusoids was present following the blood transfusion. The sinusoids became widely dilated and marked congestion was present. Absolute stasis occurred forty-five minutes to one and one-half hour prior to the cessation of respirations.

The length of life of the animals in this series was prolonged definitely (Fig. 3, *c*) and two to four additional doses of pentobarbital sodium were needed during the course of the experiments. Even when complete stasis was present, the animal was restless and needed more anesthetic. The respiratory rate went as high as 160 to 240 a minute and remained elevated for one to two hours before the respirations ceased. One animal lived for the six-hour period of observation without exhibiting any capillary stasis and the hemoconcentration in this animal was not as marked as in the remainder of the group.

The legs were much more edematous than usual, the circumference at the tibial tubercle showing an increase of 1.4 to 1.8 cm. rather than the increase of 0.7 to 0.8 cm. seen in the usual untreated type of rubber band trauma.

c. Blood plasma (Table IX).—Blood plasma was first made by mixing 8 to 12 c.c. of blood with 0.5 to 1.0 c.c. of 10 per cent solution of heparin. The blood then was centrifuged for twenty minutes and the supernatant plasma was removed. Blood plasma, 3 to 3.5 c.c., was given intravenously at the time the rubber bands were cut. Considerable hemorrhage was encountered on some occasions so that subsequently a 5 per cent solution of heparin was used in this procedure with better success.

(1) Mesentery: The capillary response resembled that found after intravenous administration of Ringer's solution. Immediately following the injection of plasma, a few newly functioning capillaries appeared

TABLE IX

EFFECT OF INTRAVENOUS INJECTION OF BLOOD PLASMA WHEN RUBBER BANDS WERE CUT

NUMBER	WEIGHT (GM.)	DURATION OF LIFE	DIFFERENCE IN RED BLOOD CELLS*	DIFFERENCE IN HEMATOCRIT (PER CENT)	CAPILLARY RESPONSE
1	134.6	6°+	0.52	13	Mesentery: Not different from the group treated with Ringer's solution except in Animals 1, 2, 8, and 12 which lived for 6 hours, and their capillary circulation returned to normal Liver: As in Table III, except those animals that lived, in which the sinusoidal circulation remained very active
2	126.5	6°+	0.29	9	
3	116.5	2°14′	2.20	32	
4†	152.6	2°12′	0.21	13	
5†	109.5	1°58′	−0.56	0	
6	118.2	3°3′	2.51	21	
7†	101.4	3°27′	0.33	11	
8	144.5	6°+	0.83	11	
9†	128.5	1°53′	1.81	25	
10	122.5	4°8′	1.42	13	
11	111.0	3°3′	1.74	17	
12	120.4	6°+	0.53	14	

*Millions per c. mm. of blood.
†Denotes hemorrhage.

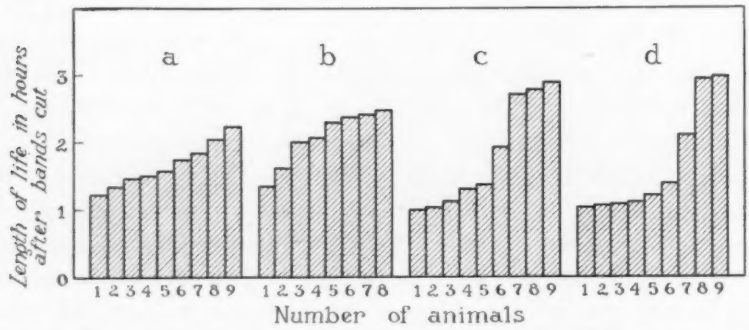


Fig. 4.—Effects of adrenal cortical hormone alone. *a*, Animals given 1 c.c. of Ringer's solution subcutaneously on three consecutive days, then shock induced; *b*, animals given 1 c.c. of adrenal cortical mixture in Ringer's solution subcutaneously on three consecutive days, then shock induced (each cubic centimeter of adrenal cortical mixture equals 75 Gm. of the gland); *c*, treated with 2 c.c. of sesame oil subcutaneously two and one-half hours before shock was induced; *d*, treated with 2 c.c. of adrenal cortical extract in sesame oil two and one-half hours before shock was induced. (Such a dose was equal to 1 mg. of compound E and 1,500 Gm. of the gland.)

and a slight slowing of the circulation often was seen. In a few instances, this effect was temporary and the circulation soon became normal. In the others the decreased circulatory speed was maintained and one to two hours prior to death the circulation became sluggish but stasis was a terminal phenomenon rather than an early occurrence as seen with the use of whole blood.

In those animals in which hemorrhage occurred, dilatation was present, but few cells were present in the terminal stages, resulting in a vacant appearance of the capillaries and a pale appearance of the region in general

(2) Liver: All of the sinusoids became very active, maintaining a rapid circulation, but were not markedly congested. The usual response of slowing of the circulation one hour to one hour and a half prior to

death was seen with terminal stasis in those animals that died, whereas in those that lived the sinusoidal circulation remained quite rapid.

In the cases of hemorrhage, although congestion did not develop, the paleness seen in the mesentery was not present.

The lives of four of these animals (a third of the group) persisted for the six-hour period of observation and those that died needed two to four additional doses of pentobarbital sodium (Fig. 3, *d*). The abdomen of one animal was closed after the specimens for hematocrit and cell counts were taken by cardiac puncture through the diaphragm and this animal was living at the end of two days with increasing edema.

There was the usual increase of the size of the legs of this group as observed in all the animals treated with intravenous fluids.

There was no difference in the respirations of the untreated group, those treated with Ringer's solution, or those treated with blood plasma.

6. Adrenal Cortical Hormone With Rubber Band Type of Shock

This is illustrated in Fig. 4. Thirty-six animals were divided into four groups of nine animals each.

The animals in Group *a* received 1 c.c. of Ringer's solution subcutaneously on three consecutive days, while those in Group *b* received 1 c.c. of adrenal cortical extract mixture (667-1 Kendall's laboratories), in which each cubic centimeter was equal to 75 Gm. of the gland, subcutaneously on three consecutive days. The last dose in all cases of Groups *a* and *b* was given one hour before the rubber bands were cut on the third day. One animal in Group *b* died from the effects of administration of pentobarbital sodium at the time of application of the rubber bands.

There was a suggestive increase of the length of life of the animals in Group *b* over those in Group *a*, but certainly nothing conclusive (Fig. 4, *a* and *b*).

The animals in Group *c* were given 2 c.c. of sesame oil subcutaneously two and one-half hours after the bands were applied and those in Group *d* were given 2 c.c. of adrenal cortical extract in sesame oil subcutaneously at the same time. (Two cubic centimeters of this mixture was equal to 1 mg. of compound E and equal also to 1,500 Gm. of the gland.) The bands were left on for a total of five hours.

There was no demonstrable difference between the two groups in respect to length of life after the bands were cut (Fig. 4, *c* and *d*).

SUMMARY AND CONCLUSIONS

1. A comparison of the effects of histamine and shock on the capillary bed with the normal capillary circulation has been presented.

2. Histamine, when applied locally to the mesentery and liver of the rat, had no demonstrable effect on the capillaries. Very definite capillary effects were observed when histamine was given in large doses (12 to 20 mg. of the base per 100 Gm. of body weight) by the intra-

venous route. When given rapidly into the veins, 27 to 33 mg. of the base per 100 Gm. of body weight was found to be the lethal dose.

3. In the rat, shock was produced by intestinal manipulation, exposure of intestines to cold, and occlusion of the circulation to the hind limbs by means of rubber bands.

4. The causation of the rubber band type of trauma was studied from three viewpoints: namely, as being due to (a) early toxic effects on the capillaries, (b) bombardment of sensory impulses from the traumatized region, or (c) local loss of fluid into the damaged region.

a. Since large doses of histamine were necessary to cause death of the animal and also since histamine is removed rapidly from the blood stream of the rat, it would seem that histamine was not the causative factor in this type of shock.

No immediate capillary dilatation was seen to occur in the mesentery or hepatic capillaries when the rubber bands were released. When the loss of fluid was minimized by wrapping the legs tightly, the capillary bed did not differ from that of the normal control animal over a six-hour period of observation following the cutting of the bands. Thus, there was no positive evidence for the liberation of a toxic substance causing immediate capillary damage in this type of shock.

b. Section of the lumbar portion of the spinal cord with needling of the distal segment of the cord did not prolong the lives of the animals in the rubber band type of trauma and, therefore, the bombardment of sensory impulses from the traumatized region would seem to play a minor role in the causation of this type of shock.

c. Wrapping the hind legs tightly with adhesive tape just before the rubber bands were cut, minimizing the local loss of fluid, did prevent the onset of shock as was confirmed by the normal respiratory rate, the normal capillary circulation, the general condition of the animal, and the normal results of hematocrit and red blood cell studies.

Temporary wrapping of the legs for one hour after the bands were cut was not of any benefit.

5. Fluids were given intravenously to the animals at the time the rubber bands were cut. In all these cases, there was much more edema in the legs and pelvis than was seen in the untreated occlusive circulatory type of shock.

a. Ringer's solution enabled the animals to live a little longer than the controls and necessitated one additional dose of pentobarbital sodium.

b. Whole blood permitted the animals to live longer than the controls, necessitating two to four additional doses of pentobarbital sodium. One animal in this group lived for the six-hour period

of observation. Accompanying the prolonged period of capillary stasis was the persistence of a very rapid respiratory rate for about one hour prior to the death of the animals.

c. Blood plasma allowed the animals to live longer than the controls, one third of the animals living for the six-hour period of observation. This fluid was definitely the most efficacious in preventing the onset of shock.

6. Adrenal cortical hormone, used alone, was of no effect in prolonging the lives of the animals undergoing the rubber band type of trauma.

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THE EFFECTS OF CONCENTRATED SERUM IN CONTRAST TO ISO-OSMOTIC PLASMA UPON NORMAL AND DEHYDRATED DOGS IN SHOCK*

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HUMAN plasma and serum are being prepared and used extensively at the present time. It has been advocated by some[1-3] that concentrated plasma protein solutions should be used in the treatment of shock; others[4] have reported that concentrated and normal protein solutions are of equivalent value in the treatment of experimental post-hemorrhagic shock; still others[5] have found that concentrated plasma is of no prophylactic or therapeutic value in experimental shock. In view of these conflicting reports and in view of the use of large amounts of concentrated plasma protein solutions in the armed forces, a thorough understanding of the comparative effects of concentrated and normal plasma is needed. Furthermore, in view of the fact that dehydration of combatants is almost inevitable, it is necessary to evaluate the therapeutic effects of normal and concentrated plasma or serum in relation to the state of hydration of the individual. The purpose of this preliminary communication is to present our laboratory experience on the use of normal and concentrated plasma or serum in normal and dehydrated animals. On the basis of this experience, we feel that concentrated blood protein solutions must be used circumspectly, especially in dehydrated individuals.

Shock was produced in dogs by graded hemorrhage, a procedure which has been found to deplete fluid reserves severely.[6] The state and severity of shock was judged by general condition, circulating time, plasma volume, hematocrit, carbon dioxide content of the plasma, and blood pressure. Essentially two groups of dogs were studied, each group containing at least twelve animals: (a) Normal dogs transfused with normal or with fourfold concentrated canine serum or plasma; (b) dehydrated dogs transfused with normal or with fourfold concentrated canine serum or plasma.

An equivalent amount of protein was restored to all animals, the only difference in the infusions being the water content. Normal serum or plasma was infused to these animals in an amount equal to the total volume of blood removed during the graded hemorrhage at a rate of 50 to 100 c.c. per minute. The fourfold concentrated solutions were given at a rate of 50 c.c. per minute in an amount equal to approximately

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one-fourth of the total volume of blood removed. The protein content of the concentrated serum and plasma varied from 15 to 20 per cent, that of the normal from 4 to 6 per cent. In several instances, as others have noted,[7] where concentrated and even normal plasma was administered rapidly, the animals exhibited severe tetany, evidently due to a lowering of the free calcium ion concentration by the considerable amounts of infused sodium citrate. No such effects were observed when normal or concentrated serum was given at comparable rates. The results of the experiments are summarized below.

1. Blood Pressure.—The blood pressure rose to near normal levels in all four groups of animals, but with normal serum or plasma the response was more rapid and more pronounced. Those receiving the normal material responded maximally in four to fifteen minutes, after injection, compared to fifteen to thirty minutes in those receiving the concentrated infusion. Another significant observation was the apparent overburdening of the heart by rapidly infused concentrated solutions. This was manifested by a transient drop in the diastolic pressure and slowing of the heart during, and shortly after, such infusions.

The animals treated with concentrated solutions were unable to maintain their blood pressures when subsequent small amounts (10 to 20 c.c.) of blood were withdrawn one hour after the infusion.

2. Carbon Dioxide Content of the Blood.—The carbon dioxide content seemed to be a far more accurate criterion for the degree of shock, extent of recovery, and prognosis than the blood pressure. Often a dog whose blood pressure and circulating time had returned to normal after infusion had a carbon dioxide content of 10 to 25 volumes per cent and, subsequently, its condition deteriorated.

Following hemorrhage, the dehydrated dogs usually developed more rapidly a severe degree of shock as indicated by a lower CO_2. After infusion, in the dehydrated dogs the CO_2 did not return as well as in the normal animals. In general, the effect of normal serum or plasma was superior in both groups to that of the concentrated solutions, as reflected by the higher level to which the CO_2 rose following administration of the former.

3. Plasma Volumes.—Plasma volumes, in general, were increased significantly in all four groups of animals following infusion. Despite the increase in plasma volumes, the dogs receiving the concentrated infusions failed to survive as long as those animals receiving normal infusions. This was particularly pronounced in the dehydrated animals. Apparently, the gain in plasma volume and the improvement in circulation following infusions with concentrated solutions were achieved by an extreme and unphysiologic withdrawal of extravascular fluid and, consequently, damage to vital organs and functions may have resulted. It would, thus, seem paradoxical to restore circulating volume and at the same time severely damage the tissues by a therapeutic measure.

4. Clinical Conditions and Survival Times.—The clinical condition and survival time of the normal as well as the dehydrated dogs infused with normal plasma or serum was distinctly superior to the comparable groups receiving the concentrated material.

CONCLUSIONS

1. Concentrated plasma or serum was found to be less effective in the restoration from shock and in maintenance of life thereafter than was normal plasma or serum.

2. The state of hydration was an extremely important factor in the ability of an animal to withstand shock and its response to therapy. Dehydrated animals developed a more profound state of shock. Their response to plasma or serum infusions, and particularly to concentrated solutions, was decidedly poorer than that of normal animals.

3. Therefore, it can be anticipated that when concentrated plasma or serum is administered, and particularly to dehydrated individuals, the degree and duration of improvement are apt to be incomplete and transient. If only concentrated serum or plasma is available, additional normal plasma or saline solution should be administered simultaneously, or at the earliest possible moment.

4. The amount of citrate contained in plasma may be sufficient to produce tetany if administered rapidly in large amounts.

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SURGICAL EXCISION OF PRIMARY TUMOR OF LIVER (HARMARTOMA) IN INFANT SEVEN MONTHS OLD WITH RECOVERY

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PRIMARY tumor of the liver in infants is extremely rare but various pathologic types have been described, the most common and most malignant being the primary liver cell carcinoma. Small hemangiomas of the liver are found occasionally at autopsy as incidental findings. They rarely produce symptoms of clinical significance. Of the benign tumors reported, the solitary adenoma is best known; this usually arises from the right lobe of the liver and may reach considerable size. Hamartoma of the liver in infants is another type of benign tumor described in the foreign literature by two authors, each reporting one patient, the diagnosis being made at autopsy in each case. Dr. Ladd of Boston has operated upon two such patients, one of whom survived the operation. Both patients were under one year of age. It has been emphasized by Albrecht, that in the "hamartumors," a very different developmental disturbance proceeds, namely, an excessive development of one tissue of one organ or the retention of the tissue in an embryonal state. Ladd has also stated that this tumor is really not neoplastic but should be regarded rather as development of abnormally placed liver tissues which are attempting to form liver substance but yet not attaining the complete pattern of the normal organ. The mass contains imperfectly formed liver lobules, biliary ducts, and possibly blood vessel networks in a purposeless arrangement. Mitotic figures are rare, there is no tendency to invasion of the surrounding tissues, and metastases do not occur. The mass may be encapsulated and merge with the liver substance. The following case is presented.

CASE REPORT

The patient, a white female, 7 months old, was first seen on Jan. 16, 1942. Five weeks previous to this date, a questionable mass had been noticed midway between the right upper and lower quadrant of the abdomen. Since the first examination, the mass had increased in size but produced no symptoms except occasional vomiting. There had been no loss of weight. From the clinical findings it was thought that this mass might be either a Wilms' tumor of the kidney or a tumor of the liver.

An intravenous pyelogram showed the kidney, pelvis, and calices to be normal but there was a questionable enlargement of the right lobe of the liver. Subse-

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Fig. 1.—Retrograde pyelogram reveals a normal appearance of the right kidney, pelvis, and calices but the right ureter is displaced medially.

Fig. 2.—Film taken after evacuation of portion of barium enema. Note the density which appeared continuous with the liver shadow; the liver border is drawn in with solid line.

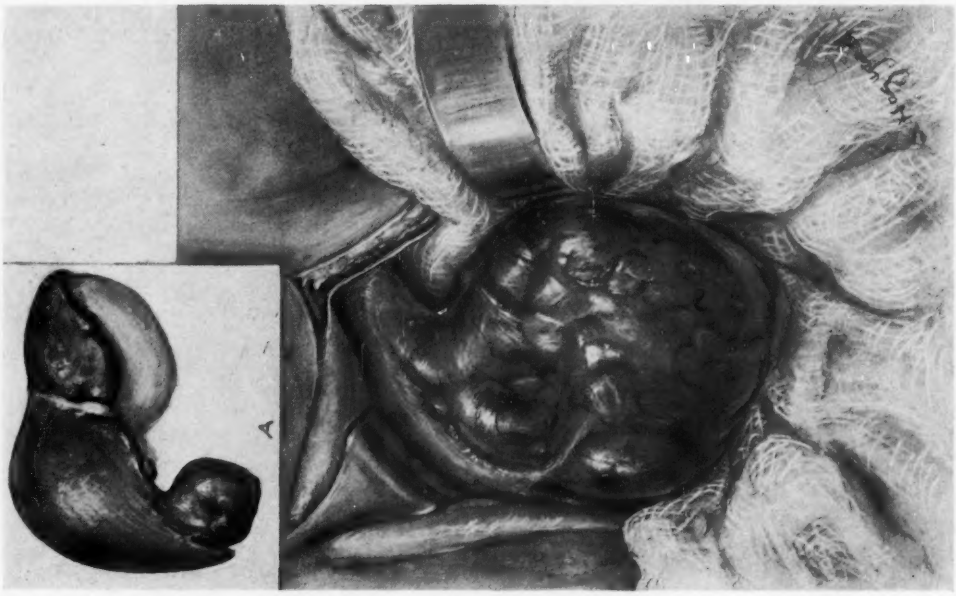

Fig. 3.—*A*, Illustration of size and location of liver tumor. *B*, Drawing which demonstrates method of isolating tumor preliminary to excision.

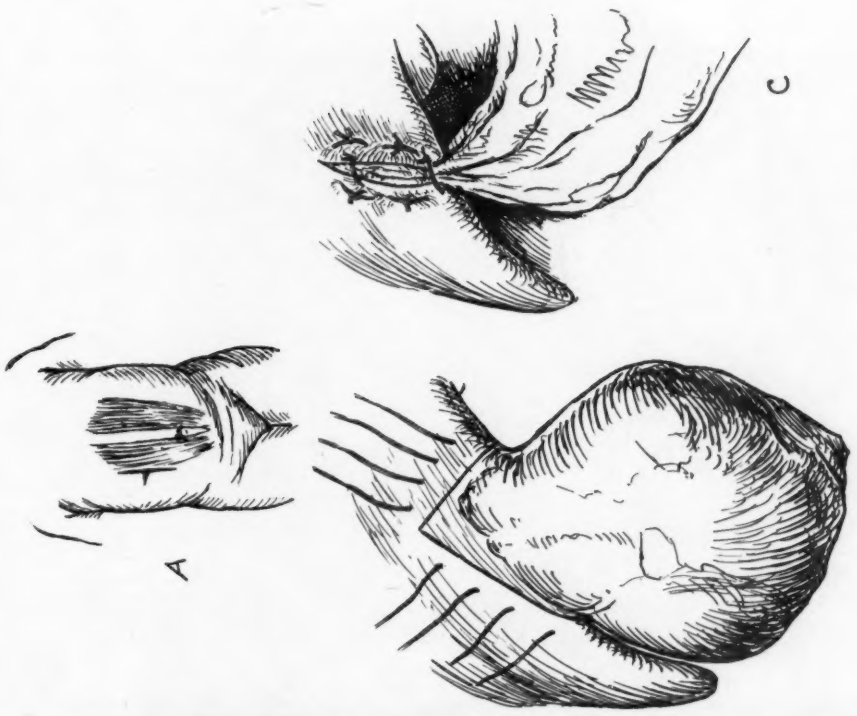

Fig. 4.—*A*, Type of incision. *B*, Illustration of method of inserting sutures and the line of excision of tumor. *C*, Omentum placed in liver wound and fixation of omentum with chromic sutures.

Fig. 5.—The gross specimen removed at operation had the appearance of liver tissue but was encapsulated. The weight of the tumor was 60 Gm.; the normal liver of a baby this age weighs approximately 250 Gm.

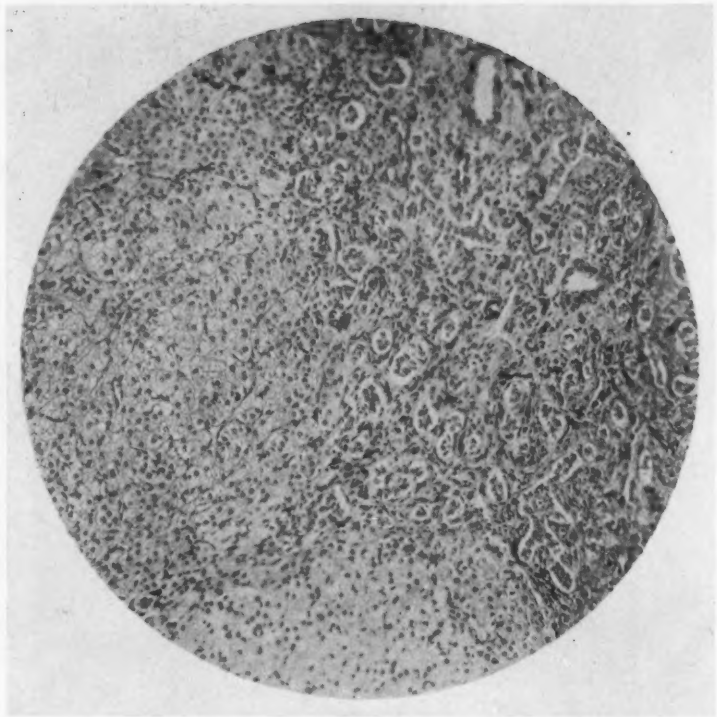

Fig. 6 (L. P.).—There is a Y formation of bile-duct proliferation and in the right half of the field are multiple vacuolated liver cells.

quently, the patient was cystoscoped and a filament-like catheter was introduced into the right ureter and was injected with an opaque media.

Following the cystoscopy and pyelogram studies, a barium enema showed the ascending colon and cecum to be displaced medialward, underlying the spinal area.

From these findings, a diagnosis of probably primary tumor of the right lobe of the liver was made and surgical intervention advised.

On Jan. 21, 1942, a laparotomy was performed under ether anesthesia. The peritoneal cavity was entered through a high right pararectus incision, with later conversion to a T type of incision. On introducing the hand into the right upper quadrant, a mobile tumor was palpated at the outer margin of the right lobe of the liver and it could be delivered into the operative wound. On gross examination, its surface was quite vascular with large veins on the anterior surface and was classified as a hepatoma. Gauze pads were placed in the right upper quadrant isolating the tumor proper (Fig. 3).

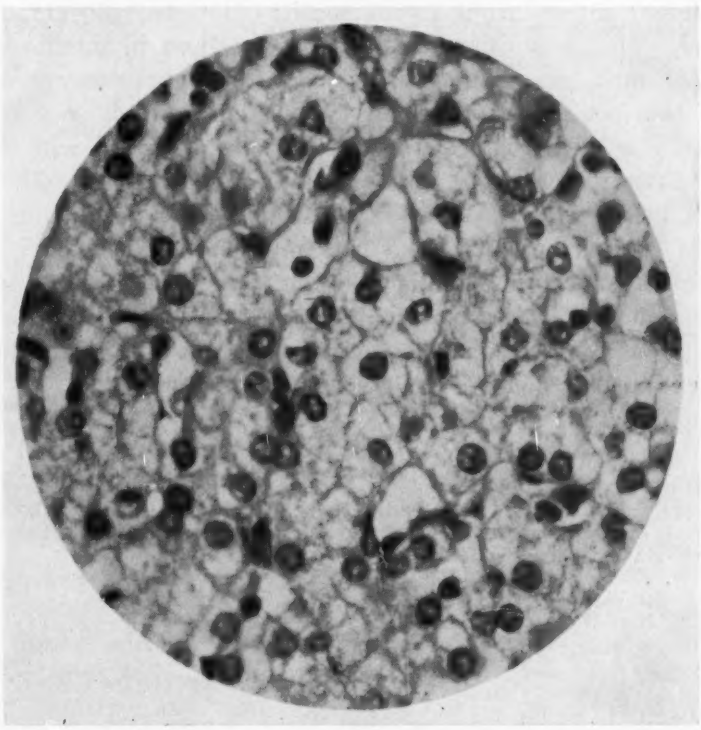

Fig. 7 (H. P.).—Many large hepatic cells with oval or round nuclei are seen; there is vacuolization of the liver cells and no regular arrangement. No mitotic figures are present.

Through-and-through chromic catgut sutures were placed in the liver substance approximately 0.5 cm. away from the borders of the tumor. The tumor was excised with the cautery knife as illustrated in Fig. 4, *B*. Hemostasis was accomplished by touching the raw surface of the liver with the Bovie coagulating blade. The free edge of the greater omentum was tucked into the operative defect in the liver and anchored in place by the catgut sutures (Fig. 4, *C*). At this point, the patient showed evidence of moderate surgical shock which was quickly overcome by a transfusion of 100 c.c. of blood. The abdomen was closed in layers using 0 chromic for the peritoneum, and interrupted silk for the fascia and skin. The postoperative course was uneventful and the patient was discharged on the tenth day after operation. On the last examination, May 2, 1942, she was in excellent health.

The microscopic studies as reported by Dr. Plinn F. Morse were as follows. This tumor consisted of irregular lobules of large liver cells arranged in cords with clear vacuolated or acidophilic granular cytoplasm, round to oval nuclei, and a few definite nucleoli. There was moderate fatty degeneration of individual liver cells. The lobules were separated by dense fibrous connective tissue bands in which there was a marked proliferation of the bile ducts with some infiltration into the surrounding hepatic parenchyma. These bile duct radicles were evidenced by cuboidal cells with prominent nuclei, clear cytoplasm, and small tubules with empty lumina. There was no bile stasis. Distinct mitotic figures were not seen in either the hepatic or bile duct cells.

Microscopic Diagnosis.—Liver cell hamartoma or solitary hepatoma (Ewing).

SUMMARY

Complete excision of a primary encapsulated tumor of the liver (hamartoma) in an infant seven months old, with recovery, has been described. The recognition of tumors of the liver in infants is important. All such patients deserve exploratory laparotomy because, in spite of the fact that liver tumors in infants carry a poor prognosis, occasionally a benign tumor such as the one described will be found. Complete surgical removal will offer a good prognosis. Hamartoma tumor of the liver can be considered benign for the following reasons: (1) It is well encapsulated and has embryonal characteristics, (2) it shows no tendency to invade neighboring tissue, (3) on microscopic examination no mitotic figures are found, (4) metastases do not occur, and (5) symptoms arise only from the progressive growth of the tumor with subsequent displacement of neighboring structures.

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GASTRIC SECRETORY DEPRESSANT IN GASTRIC JUICE*

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THE discovery of a gastric secretory depressant factor in gastric juice of patients with achlorhydria and gastric carcinoma,[1] and achlorhydria and pernicious anemia[2] was described in previous reports. The acid gastric juices of patients not presenting these diseases and which were employed in control studies were also found to contain this factor but in obviously much lower concentrations. This led to the hypothesis that the factor was perhaps a normal constituent of gastric juice and was present in increased concentrations in the achlorhydric gastric juices of patients with the above diseases. Further studies were carried out to obtain more data on this question.

METHODS

The same procedures were followed as in the previous work. Subtotal gastric pouches cannulated to the exterior were made in dogs. A month or more later the animals received intravenous injections of neutralized human gastric juices (10 to 20 c.c.) in order to immunize them from febrile reactions due to such injections, since rapid rises in temperature will themselves induce a transitory achlorhydria. Some animals do not become fever resistant as a result of these injections but the acid-secreting mechanism of the gastric pouch does become immune to the inhibitory influence of fever.

With the animals thus prepared, experiments were conducted as follows: The animal, placed upon a table, is fed lean meat and when vigorous secretion from the cannulated pouch obtains, the test solutions or suspensions are injected intravenously and the gastric juice then collected at 10-minute intervals, the volume is noted, and free and combined acidity are titrated, using $\frac{1}{10}$ N – NaOH and Toepfer's reagent and phenothaleine as indicators. Frequent rectal temperatures are obtained to ascertain any unusual rise in temperature that might invalidate the experiment. The animals are also fed meat, forcibly if necessary, at 30- to 40-minute intervals to insure continued physiologic stimulation for secretion of gastric juice. If, as a result of an injection, achlorhydria occurred the experiment was continued until there was a return to preinjection levels of volume and acidity. As in the previous studies, the arbitrary method for recording results was as follows: +, reduction in 10-minute secretion volume to 3 drops or less for at least

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20 minutes with persistence of free acid; ++, achlorhydria for 10 to 20 minutes; +++, achlorhydria for 30 to 50 minutes; ++++, achlorhydria for 60 minutes or more.

Precipitation of the Active Factor.—Numerous attempts were made to obtain an active fraction (containing the secretory depressant) of the gastric juice by various types of precipitation. It was observed that an addition of four volumes of absolute alcohol to neutralized juice yielded a white flocculent precipitate which contained the secretory depressant. This method was employed in all of the following studies. the quantity of the precipitate obtained varied for equal volumes of juice. After addition of the alcohol, the mixture was placed overnight in the refrigerator. The next morning as much as possible of the clear supernatant liquid was decanted and the remainder centrifugated. The precipitate was then dried in air and resuspended in 10 to 20 c.c. distilled water for injection.

SERIES I

To Determine Whether the Gastric Secretory Depressant Factor is Present in Dog's Gastric Juice.—Pouch gastric juice was collected from a given animal which was fed meat. The samples were pooled and stored in a large bottle. When the desired volume was obtained it was neutralized to litmus with NaOH (care being taken not to reach alkalinity because this frequently inactivated the factor) and precipitated as described above with alcohol. The precipitate of a small volume was injected as a first experiment, to be followed in a few hours on the next day by injection of the precipitate of a much larger volume. When achlorhydria developed, the latent period varied from twenty to fifty minutes, sometimes longer. In each case the precipitate was obtained from the juice of the dog used in the experiments.

The results are summarized in Table I. They show that the smaller or moderate doses were without effect but that the precipitates of large quantities of juice contained sufficient of the factor to cause transitory inhibition of secretion volume and disappearance of acidity. The prolonged achlorhydria of five hours and twenty minutes observed in one experiment is quite unusual. The negative experiments, five of a total of fourteen where 800 c.c. or more of the juice was used, suggests a marked variation in the concentration of the factor in the pouch juice obtained.

SERIES II

To Observe Whether the Gastric Secretory Depressant Is Present in Large Quantities of Neutralized Acid Human Gastric Juice From Patients Not Presenting Gastric Cancer or Pernicious Anemia.—The juice was obtained from patients subjected to routine histamine tests for gastric secretion in both the outpatient and hospital divisions. Only acid juices were employed and these were filtered through gauze before precipitation. When quantities exceeding 150 c.c. were employed, several samples from different patients were pooled.

In this series of observations "one dose" was arbitrarily chosen as the 80 per cent alcoholic precipitate of neutralized juice, the volume of the juice being equal to 1 c.c. per kilogram weight of the dog employed. The weights of the animals employed varied from 7 to 12 kg. The results of the experiments are summarized in Table II. The progressive increase in incidence of positive experiments paralleling the increase in volume of juice whose precipitate was injected indicates the presence of the gastric secretory depressant in relatively low concentrations in the gastric juice. Fig. 1 is a graph showing secretory depression following intravenous injection of the alcoholic precipitate of 200 c.c. of pooled samples of acid human gastric juice. Further experience showed that the 80 per cent alcoholic precipitate of 500 c.c. of neutralized acid human juice produced transitory achlorhydria in the pouched dogs in over 90 per cent of the experiments, of which more than twenty-five were performed.

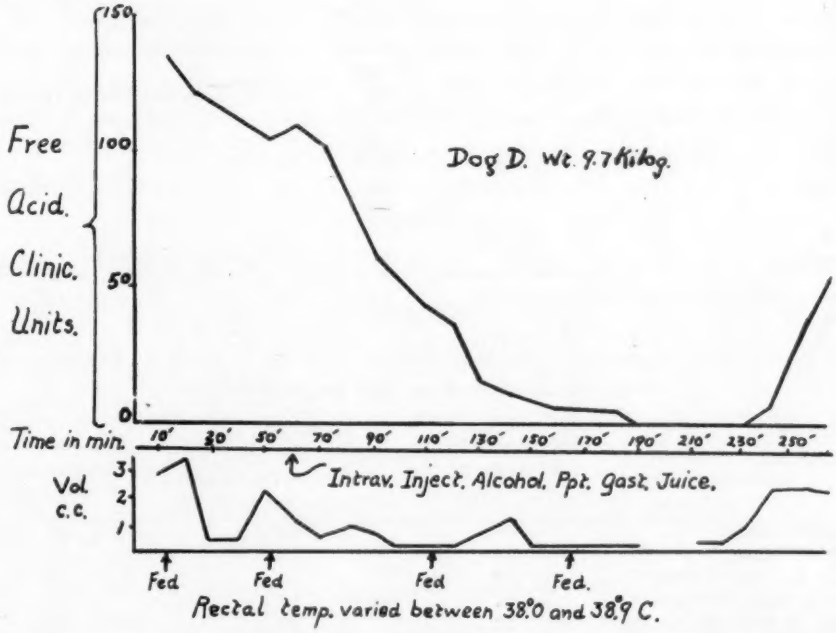

Fig. 1.—Graph showing reduction of acidity and finally transient achlorhydria, with depression of volume of secretion of dog's gastric pouch following intravenous injection of 200 c.c. of water in which was suspended an 80 per cent alcohol precipitate of 200 c.c. of neutralized acid human gastric juice (pooled samples obtained by histamine stimulation, the individuals not presenting pernicious anemia or gastric carcinoma). In this experiment the latent period for the development of achlorhydria following injection of the precipitate of gastric juice was unusually prolonged.

SERIES III

To Observe the Presence of the Gastric Secretory Depressant in Human Achlorhydric Gastric Juice From Patients not Presenting Gastric Carcinoma or Pernicious Anemia.—The achlorhydria juices were obtained in a similar manner as for Series II described above. Because the volumes of such juice obtained from a given patient are not as large as where acid juice is secreted, experiments with large volumes

were not performed. The results obtained are summarized in Table III. The incidence of positive experiments with smaller doses is appreciably greater than that obtained with comparative volumes of samples of

TABLE I

OBSERVATIONS ON THE INDUCTION OF ACHLORHYDRIA IN DOGS BY 80% ALCOHOL PRECIPITATE OF THE DOG'S OWN JUICE

DOG	RESULTS WITH PPT. OF SMALL VOLUME		RESULTS WITH PPT. OF LARGER VOLUMES	
	C.C. OF SAMPLE	ACHLORHYDRIA	C.C. OF SAMPLE	ACHLORHYDRIA
Lady	10	–	115	–
Wal.	12	–	78	–
Pep.	10	–	80	–
Rom.	15	–	500	–
Lady	12	–	600	–
Wal.	12	–	800	+++ (40 minutes)
Wal.	12	–	1000	++ (20 minutes)
Osw.	10	–	900	+++ (40 minutes)
Wal.	12	–	900	+++ (40 minutes)
Ging.	12	–	1000	++ (10 minutes)
Wal.	12	–	1000	–
Rom.	15	–	1000	++++ (5 hours, 20 minutes)
Rom.	15	–	1000	–
Wal.	12	–	1000	–
Wal.	12	–	1000	–
Longf.	12	–	1000	+
Rom.	12	–	1000	+
Ging.	12	–	1000	–
Longf.	12	+	1000	++++ (90 minutes)

TABLE II

ACHLORHYDRIA PRODUCED IN DOGS BY INJECTION OF 80% ALCOHOL PRECIPITATE OF NEUTRALIZED HUMAN ACID GASTRIC JUICE*

QUANTITY OF JUICE PRECIPITATED	NO. OF EXPERIMENTS NEGATIVE	NO. OF EXPERIMENTS SHOWING ACHLORHYDRIA OR MARKED SUPPRESSION OF SECRETION VOLUME	PER CENT OF EXPERIMENTS "POSITIVE"
Single "dose"	64	16	20
Triple "dose"	29	14	33
Four to five "doses"	12	9	42
Six to eight "doses"	24	17	55
Nine to sixteen "doses"	12	20	66

*From patients not presenting gastric carcinoma or pernicious anemia.
One "dose" = precipitate of volume of juice equal to 1 c.c. per kilogram weight of the animal employed.

TABLE III

ACHLORHYDRIA PRODUCED IN DOGS BY INJECTION OF 80% ALCOHOL PRECIPITATE OF ACHLORHYDRIC HUMAN GASTRIC JUICES*

QUANTITY OF JUICE PRECIPITATED	NO. OF EXPERIMENTS NEGATIVE	NO. OF EXPERIMENTS SHOWING ACHLORHYDRIA OR MARKED SUPPRESSION OF SECRETION VOLUME	PER CENT OF EXPERIMENTS "POSITIVE"
Single "dose"	20	10	30
Triple "doses"	19	20	52

*From patients not presenting gastric cancer or pernicious anemia.
Each experiment represents one sample of juice from one individual patient.

acid juice suggesting a greater concentration of the depressant factor associated with achlorhydria.

Some studies were conducted upon the properties of the secretory depressant; it was observed to be destroyed by boiling for five minutes; it was found not to dialize across a cellophane membrane; alkalinization of the juice inactivates the secretory depressant.

DISCUSSION

Extensive control experiments have been performed and reported[1, 2] to show that the gastric secretory depression observed in the experiments is not artifactual incident to intravenous injection of gastric juice. The nature and significance of the gastric secretory depressant demonstrated in gastric juice of both dogs and humans remains obscure, but it is suggested that it may represent a normal physiologic mechanism for gastric secretory inhibition. Support for this hypothesis is afforded by the fact that it appears to be present in greater quantity in achlorhydric juice. An alternate explanation is that it is secreted at more or less constant rate by some cells of the gastric mucosa and that in achlorhydria it appears to be more concentrated in the juice because the total volume of the latter is reduced as compared with stomachs secreting acid gastric juice.

SUMMARY

By a standard physiologic method for the study of factors affecting gastric secretion, a gastric secretory depressant has been demonstrated to be present in dog's gastric pouch juice, acid human gastric juice, and achlorhydric gastric juice from patients not presenting gastric cancer or pernicious anemia.

Taking into account previously recorded studies, this factor appears to be present in lower concentrations in the above types of juice than in the achlorhydric gastric juice of patients with carcinoma of the stomach or with pernicious anemia.

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THE HALSTED RADICAL MASTECTOMY

Five-Year Results in 246 Consecutive Operations at the Same Clinic

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THE effectiveness of a method of treating cancer of the breast can best be judged by following its results in a consecutive series of patients over a period of five years and more. This report deals with such a series and includes 240 patients, all cared for in the same institution. It is an extension of a report made by R. D. McClure, in 1931.[17] In each case the primary growth was removed by radical mastectomy, following the method of Halsted. In eleven cases a subsequent carcinoma was found in the opposite breast. Six of these patients were subjected to a second radical mastectomy, while five had a simple mastectomy. All 240 patients were operated upon between 1918 and 1935 inclusive, so that the follow-up of the living patients covered at least five years. In only six cases, however, (2.5 per cent) are our follow-up records incomplete.* Most of these patients had evidence of metastases when last seen, and for statistical purposes have been considered as dead from carcinoma.

The criteria of operability were much the same as in other clinics. Radical operations were not advised in patients with known distant metastases, advanced local breast cancer, or ulcerating lesions, or in patients in poor general condition. Thirteen cases involving demonstrable supraclavicular metastases were operated upon, although this complication usually was considered a criterion of inoperability. Deep fixation of the carcinoma to the pectoral fascia was not considered a contraindication in the absence of ulceration.

The average age of the group of 240 patients was 51.2 years, 28 and 77 years being the extremes. In 75 cases the ages of the patients fell in the fifth decade, while the sixth and seventh followed closely, with 69 and 47 cases, respectively. Age did not appear to affect the percentage of cases with axillary node involvement nor did it appear to affect the percentage of five-year survivals to any significant degree (Table I). This is similar to Shore's[21] findings at St. Luke's Hospital in New York.

Only one case in this series was a male (0.45 per cent), a lower incidence than that commonly reported in similar series. Horsely[12] reported 4 cases of carcinoma of the breast in the male to 359 in the female, or 1.1 per cent. Stout[24] found the proportion of 6 to 349, or 1.7 per cent, while Judd and Morse[13] found 17 cases of carcinoma of the male breast to 1,751 cases of carcinoma of the female breast, or 0.9 per

*For the high percentage of patients followed, thanks are due the Detroit Board of Health and its field worker, Mrs. Helen Andries, and also Miss Ruby Cook, who handled all correspondence and recording.

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cent. Judd and Morse concluded that carcinoma of the male breast was a highly malignant type of neoplasm and that radical operation was not as satisfactory as in females. The patient in our case lived seven years and ten months following operation and manifested several sites of metastases, among them the tonsil and the cervical and axillary nodes.

TABLE I

CASES GROUPED ACCORDING TO AGE

AGE	20-29	30-39	40-49	50-59	60-69	70-79	TOTAL
Number of cases	1	36	75	69	47	12	240
Percentage	0.4	15.0	31.2	28.7	19.5	5.0	100
Number of cases with axillary metastases	1	26	48	40	28	6	149
Percentage	100	72.0	64.0	58.0	57.0	50.0	62.1
Number of five-year survivals	0	10	40	34	19	8	111
Percentage	0	28.5	53.0	49.0	40.5	66.6	46.0

A history of trauma was elicited in 15 of the 251 tumors removed, giving a percentage of 5.9. Twenty-seven patients (11.2 per cent) stated that one of their immediate relatives had had cancer, while in 13 cases (5.4 per cent) the cancer was said to have been in the breast.

The known duration of the presenting symptoms was analyzed to determine if a higher percentage of axillary metastases was found in those patients who did not present themselves until some time elapsed after they were conscious of their disease. In those cases where the symptoms were present for a month or less, axillary metastases were present in 55.3 per cent. If the symptoms were present from one to six months, 59.8 per cent of the patients had axillary metastases, while those who let their symptoms develop over six months had axillary metastases in 62.7 per cent of the cases. The percentage of five-year survivors in each group diminished as the length of time the symptoms were present increased, regardless of whether or not axillary metastases were present (Table II). This gives added evidence to support the dictum that carcinoma should be treated early and adequately for the best results.

Lewis and Rienhoff,[15] and Kunath[14] did not find any definite correlation between the duration of symptoms and the length of life after

TABLE II

A COMPARISON OF FIVE-YEAR SURVIVALS ACCORDING TO DURATION OF SYMPTOMS

DURATION OF SYMPTOMS	AXILLARY METASTASES	NO AXILLARY METASTASES	% AXILLARY METASTASES	NO. 5-YEAR SURVIVALS		% 5-YEAR SURVIVALS	
				AXILLARY METASTASES	NO AXILLARY METASTASES	AXILLARY METASTASES	NO AXILLARY METASTASES
1 month or less	26	21	55.3	9	15	34.6	71.4
1 to 6 months	64	43	59.8	20	29	31.2	67.4
Over 6 months	54	32	62.7	14	21	25.8	65.6
No data	6						

operation. Greenough and Taylor[8] found that in their different groups of cases based on metastases, the preoperative duration of symptoms was longer in the patients that did not survive the five-year period. Their statistics, like those of Lewis and Rienhoff,[15] contain several cases with a preoperative history of a tumor for two or more years with a high incidence of five-year survivals. This is not surprising when one considers that these are low-grade malignancies, else they would not have lived long enough to be operated upon.

In comparing the two breasts as to the frequency of the primary tumor, the left breast was found involved oftener than the right, by 13.8 per cent. The right breast was involved in 106 cases, while the left in 140 cases, or 43.1 and 56.9 per cent, respectively. However, in regard to the quadrants of the breast another situation existed. The upper outer quadrant was by far the most frequent site involved. One hundred and nineteen of the tumors in this series were located in that quadrant. The second most common site for the location of tumors was under the areola. Analysis of the location of the primary tumor with reference to five-year survivals showed that the upper outer quadrant and the line directly above the areola had the lowest percentage, while the lower outer quadrant had the highest (Table III).

TABLE III

LOCATION OF TUMOR IN BREAST

LOCATION	NUMBER OF CASES	FIVE-YEAR SURVIVALS	PERCENTAGE
Upper outer quadrant	119	45	37.8
Upper inner quadrant	34	18	52.6
Lower outer quadrant	20	13	65.0
Lower inner quadrant	14	9	64.2
Under areola	40	19	47.5
Directly above nipple	8	3	37.5
Medial to nipple	2	1	50.0
No data	9	3	33.0

No correlation was found between the postoperative duration of life and the size of the tumor removed. When the various sized tumors were subdivided into groups with and without axillary metastases, a great difference in the percentages of five-year survivals was noted, which contributes more evidence to the fact that the presence or absence of axillary metastases is still our best prognostic sign. In the 246 radical mastectomies, the pathologist was able to locate metastases in the axillary nodes in 152 cases (61.7 per cent). Harrington[11] found that 61.6 per cent of the 5,830 cases he reported had axillary involvement.

Clinical examination revealed palpable axillary nodes in 145 of our cases. Of these, 111 (76.5 per cent) contained demonstrable metastases. In 97 cases where no nodes were palpable, on clinical examination, metastases were later demonstrated in 38 (39.1 per cent). This makes the error of clinical impression of axillary involvement 23.5 per cent when nodes are palpable and 39.1 per cent when no nodes are palpable.

Greenough and Taylor[8] and Shore[21] note the marked error in the preoperative diagnosis of the presence of axillary metastases and their percentage of error is almost the same as ours, namely, 32 and 34.2 per cent respectively. The above figures of error in the clinical examination of the axilla for metastases support a strong feeling we have that the value of information gained from axillary palpation is slight at best and decidedly not worth the danger to the patient from searching or repeated efforts to find lymph nodes.

The radical removal of the breast for mammary carcinoma used in this series is essentially the one developed by Halsted[9] and Meyer.[18] The Halsted skin incision was also used for the most part. Skin grafts were not performed in all cases, however, as described by Halsted. A plastic closure was used in 176 cases and the Thiersch graft in 46 cases. In 24 cases a Thiersch graft was not used, but instead a secondary pinch graft was used after a few days' convalescence from the radical mastectomy.

Local skin recurrence occurred in 15 per cent of the cases. The patients with plastic closures in this series had a local skin recurrence rate of 5.5 per cent and 16 per cent, depending upon whether or not axillary metastases were present. When a skin graft was done, the recurrence rates in the skin were 8.3 and 27 per cent (Table IV). One possible

TABLE IV

A COMPARISON OF TYPES OF CLOSURE AND LOCAL SKIN RECURRENCES

	NO. OF CASES	NO. OF RECURRENCES	PERCENTAGE
Plastic Closure:			
No axillary metastases	23	4	5.5
Axillary metastases	82	13	16.0
Skin Grafts:			
No axillary metastases	24	2	8.3
Axillary metastases	67	18	27.0
Regardless of Closure:			
No axillary metastases	97	6	6.1
Axillary metastases	149	31	20.8
Total	246	37	15.0

reason for the difference between the recurrence rates with the different closures is that the larger primary tumors, or tumors attached to skin or fascia, required larger areas of skin in the incision and by the same token were probably the most malignant neoplasms. Lewis and Rienhoff[15] reported the percentage of local recurrences in 447 radical mastectomies. They found 30.1 per cent local recurrences when the Thiersch graft was used and 39.1 per cent after the plastic closure was done. Our statistics made to determine the correlation between the amount of skin excised at operation and percentage of five-year survivals showed no correlation which could be explained on this basis. The group without axillary metastases, which had a large area of skin removed, showed the

greatest number of five-year survivals (83 per cent). However, when axillary metastases were present, the percentage of five-year survivals dropped to 21 per cent, which was even lower than the group in which the plastic closure had been done (Table V).

TABLE V

A COMPARISON OF TYPES OF CLOSURE ACCORDING TO FIVE-YEAR SURVIVALS

	NO. OF CASES	NO. OF FIVE-YEAR SURVIVALS	PERCENTAGE
Plastic Closure:			
No axillary metastases	73	49	67.0
Axillary metastases	82	28	34.0
Skin Graft:			
No axillary metastases	24	20	83.0
Axillary metastases	67	14	21.0
Regardless of Closure:			
No axillary metastases	97	69	71.0
Axillary metastases	149	42	28.0
Total	246	111	45.0

Patients with postoperative distant metastases form an interesting group for the metastases may appear at any time after the operation and frequently only after the lapse of several years without symptoms. In the case of bone metastases, pain is probably the earliest symptom and was occasionally present from four to six months before demonstrable x-ray changes could be detected. We were able to diagnose bone metastases by x-ray in 50 cases (20.8 per cent). The spine was the most frequent site of bone metastases, with the ribs next in frequency (Table VI). Metastatic lesions were found in the lungs and pleura

TABLE VI

BONES INVOLVED IN METASTASES

Spine	33	Mandible	3
Ribs	20	Scapula	3
Pelvis	16	Fibula	2
Femur	16	Tibia	1
Humerus	4	Clavicle	1
Sacrum	3	Maxilla	1
	Sternum	1	

somewhat more frequently than in the bones. These were diagnosed principally by x-ray. However, a few cases were confirmed either by post-mortem examination or microscopic examination of the pleural fluid. Fifty-eight cases (24.1 per cent) were diagnosed as having pulmonary metastases.

Edema of the arm may occur pre- or postoperatively. When present preoperatively, it is a physical sign of advanced disease. Postoperatively it may occur at any time. It was present in 69 of the cases in this series (28.9 per cent). An interesting feature concerning this was the fact that it was transitory in many cases, and in these cases it frequently

appeared about two or three months after the operation and disappeared after a few months. In a few cases the edema was permanent, but in no case was it incapacitating or disabling. In a few cases it was preceded by a postoperative axillary infection, a recurrence of carcinoma in the axilla, or a thrombophlebitis in the vessels of the arm. Stewart [22] stated that he "regarded immediate postoperative edema of the arm as a favorable sign; it indicates that the operation has been thorough, that all the lymphatic structures in the axilla have been removed, and the lymphatic drains of the arm completely interrupted. It usually disappears in from two to four months, but may last longer, and indeed be permanent."

The postoperative mortality in this series was somewhat lower than some reports and higher than those reported in some textbooks. There were seven postoperative deaths in 246 radical mastectomies (2.8 per cent). Three deaths were from pulmonary emboli and two others were patients with marked hypertension who died of myocardial failure. One death was in a 34-year-old woman who had a large breast tumor and fluid in her chest. This did not contain tumor cells and the x-ray examination of the chest did not show a definite metastasis. No post-mortem examination was done, but this patient probably had a small pulmonary metastasis which was present at the time of operation. She lived ten days postoperatively, but the course was steadily downhill. One death was in a patient who had a marked anemia preoperatively. She was given several pre- and postoperative transfusions, but these did not bring her blood count up to normal. Post-mortem examination showed subacute parenchymatous nephritis. The urine preoperatively was negative and her history was not suggestive of nephritis.

Willy Meyer[18] reported four deaths in a series of 125 radical mastectomies (3.2 per cent). Lewis and Rienhoff[15] reported twenty-five deaths following 393 radical mastectomies (6.4 per cent). Stiles[23] states he has had "one death in upwards of 150 patients operated upon." The cause of that patient's death was sepsis. He also quoted Rodman, who collected the results of 2,133 radical mastectomies and found an operative mortality of less than 1 per cent. Handley[10] commented on the low immediate mortality of the operative procedure in the following manner, "Among some hundreds of hospital cases, including cases in paying hospital wards, four deaths have to recorded." Bloodgood[4] stated that the operative mortality of radical mastectomy was less than ½ per cent if a supraclavicular dissection was not done as part of the same procedure.

An interesting finding in the follow-up of this series of 240 patients with mammary carcinoma is the high incidence of a second carcinoma. Twelve patients lived long enough following the radical mastectomy to develop a second primary malignancy in another organ or tissue (Table VII). Carcinoma of the skin, cervix, and stomach were the most common. Most of the pathologic specimens of the second malignancy were

TABLE VII

SECOND PRIMARY MALIGNANCY

DATE OF RADICAL MASTECTOMY	SECOND CANCER	DATE OF DEATH
12/29/23	Squamous carcinoma of scalp 10/20/27	7/18/29
1/28/25	Adenocarcinoma of gall bladder 8/23/33	3/ 6/36
2/28/25	Carcinoma of stomach 1/14/30	1/14/30
7/22/26	Carcinoma of cervix 4/7/37	4/29/38
1/23/26	Basal cell carcinoma of skin; post-mortem finding 9/9/36	9/ 9/36
5/26/27	Basal cell carcinoma of skin 5/31/27	3/ 2/32
1/30/28	Carcinoma of colon; post-mortem finding 1/14/31	1/14/31
1/24/30	Osteogenic sarcoma; post-mortem finding 11/29/39	11/29/39
5/23/30	Carcinoma of ovary January, 1933	January, 1933
2/12/31	Carcinoma of cervix 3/12/35	December, 1935
6/20/32	Carcinoma of bladder January, 1938	3/30/38
2/6/35	Carcinoma of stomach 10/29/36	6/13/37

examined in this hospital; those that were not were reported to us by other institutions in the course of our follow-up. As stated earlier, 11 of the 240 developed a second carcinoma in the opposite breast which could be removed either by simple or radical mastectomy, depending upon the general condition of the patient. Others developed deposits of carcinoma in the other breast along with numerous other metastases, late in the course of the disease. One may always speculate as to whether the second tumor is a new primary or a metastasis. Inasmuch as the microscopic picture of the second tumor in most of the eleven cases was quite similar to that of the first, one would be inclined to favor the theory that the tumors were metastatic.

Although the relationship between chronic cystic disease of the breast and carcinoma cannot be definitely determined by a statistical study, it is interesting to note the frequency with which it was recorded by the pathologist in the description of the breast carcinomas of this series. Twenty-eight of the 251 specimens submitted (11.1 per cent) contained chronic cystic mastitis, and in eight of the cases it appeared that the malignancy might have originated in the area so involved. An independent review of 149 cases of chronic cystic mastitis in which either a local removal of the tumor or simple mastectomy was done showed no case which later developed carcinoma. The follow-up of twenty-five of these cases extended over five years and many from two to four years. Cheatle and Cutler[6] state that breast carcinoma develops from cystiphorous desquamative epithelial hyperplasia (chronic cystic mastitis) in about 20 per cent of the cases of carcinoma. "In the remaining 80

per cent of all carcinoma of the breast it is not so easy to demonstrate the existence of a preliminary benign epithelial neoplasm and further that all signs of a preliminary cystic state are absent.'' Bloodgood[2, 3] presents the opposite point of view, believing that carcinoma does not develop more frequently in women with chronic cystic mastitis than in any other group of women in the same age group. He reports three cases of cancer which developed in 128 cases following the removal of an area of chronic cystic mastitis. Stout[24] believes there is a definite relationship between chronic cystic mastitis and carcinoma of the breast, but does not go into more detail than to make this statement. MacCallum[16] states ''carcinoma growth seems especially common as a sequel of the senile hyperplasia with cyst formation, which is often referred to as chronic cystic mastitis.''

There has been much discussion over the merits of roentgen or radium therapy in the treatment of carcinoma of the breast. When one discusses radiation therapy, however, the question comes up as to whether or not it should be given pre- or postoperatively, what dosage should be given, the location of the radiation ports, and whether it should be radium or x-ray therapy. In this series, all radiation therapy was given after a radical mastectomy. It consisted of a course of three treatments which were usually given on consecutive days. Three ports were used, namely, a supraclavicular port, one which included the operated breast area, and the third was directed to the corresponding axilla. Approximately 700 R. units were delivered to the skin with each treatment. The usual filters were ½ mm. of copper and 1 mm. of aluminum.

An attempt was made to compare groups of cases according to the amount of x-ray therapy given. The number of five-year survivals was computed for each group, depending upon the presence or absence of axillary metastases. The greatest percentage of five-year survivals was in the group with no axillary metastases and no irradiation therapy (74.4 per cent). The groups with one, or more than one, series of irradiation therapy and no axillary metastases had almost the same percentage of five-year survivals. In the three groups with axillary metastases there was a suggestive increase in the percentage of five-year survivals when x-ray therapy was used. If no irradiation was used, there was only 21.8 per cent five-year survival, while the percentage rose to 35.8 per cent and 26.8 per cent when x-ray therapy was used (Table VIII).

The cases were analyzed further to determine the effect of x-ray therapy on local skin recurrence. The series was divided into two groups, depending upon whether or not axillary metastases were present, and these were subdivided into the recurrences that had had prophylactic irradiation therapy and those that had not. Skin recurrences were much more frequent in the group that had axillary metastases (20.8 per cent) than in the group that did not (6.1 per cent). Fifty-four of

TABLE VIII

A COMPARISON OF THE EFFECT OF X-RAY THERAPY ACCORDING TO FIVE-YEAR SURVIVALS

NO. OF X-RAY COURSES	NO. OF CASES	NO. OF FIVE-YEAR SURVIVALS	PERCENTAGE
NO AXILLARY METASTASES			
0	43	32	74.4
1	38	26	68.4
2	16	11	68.7
AXILLARY METASTASES PRESENT			
0	55	12	21.8
1	53	19	35.8
2	41	11	26.8

the 97 patients without axillary nodes had x-ray therapy and of these, three (5.1 per cent) developed local skin recurrences. Among the 43 that did not have x-ray therapy, three patients (6.9 per cent) developed local skin recurrences. Ninety-four of the 149 patients with axillary metastases had x-ray therapy, and of this group 23 patients (24.4 per cent) developed local skin recurrences. Among the 55 cases which did not have x-ray therapy, eight patients developed local skin recurrences (14.5 per cent). The type of closure was not taken into consideration in studying the effect of x-ray therapy as the series was so small that it would be questionable if the percentages would give a true picture (Table IX).

TABLE IX

A COMPARISON OF THE PERCENTAGE OF LOCAL SKIN RECURRENCES WITH AND WITHOUT X-RAY THERAPY IN CASES WITH AND WITHOUT AXILLARY METASTASES

	X-RAY THERAPY	NO X-RAY THERAPY	TOTALS
NO AXILLARY METASTASES			
Number of cases	54	43	97
Recurrences	3	3	6
Percentage	5.1	6.9	6.1
AXILLARY METASTASES			
Number of cases	94	55	149
Recurrences	23	8	31
Percentage	24.4	14.5	20.8

In attempting to judge the value of x-ray therapy in this series of cases one must say that no improvement in the number of five-year survivals was noted in the cases without axillary metastases, although a decrease was found in the number of local skin recurrences. However, irradiation therapy did appear to increase the number of five-year survivals in the cases concerned with axillary metastases, but did not appear to affect the percentage of local skin recurrences.

From a review of the cases involving late metastases, either local or distant, one finds convincing evidence that it is in these cases that x-ray therapy finds its greatest usefulness. The results here are difficult to express in percentages, for many times the effects are subjective and symptomatic, but nonetheless important. Pfahler and Parry[19] reviewed

TABLE X (FROM HARRINGTON)

A COMPARISON OF SURVIVAL RATES ACCORDING TO POSTOPERATIVE IRRADIATION IN THE FOUR GRADES OF MALIGNANCY; UNILATERAL CARCINOMA IN WOMEN WITH AXILLARY METASTASIS

GROUP	3 YEARS		5 YEARS		10 YEARS		15 YEARS		20 YEARS	
	PATIENTS TRACED*	PER CENT SURVIVALS	PATIENTS TRACED*	PER CENT SURVIVALS	PATIENTS TRACED*	PER CENT SURVIVALS	PATIENTS TRACED*	PER CENT SURVIVALS	PATIENTS TRACED*	PER CENT SURVIVALS
Concerning 181 patients treated with irradiation and 100 treated without irradiation†										
With irradiation:										
Grade 1	8	100.0	7	100.0	7	71.4	4	25.0	1	0
Grade 2	143	63.6	136	47.1	112	27.7	93	22.6	16	18.8
Grade 3	615	52.4	567	34.2	432	16.2	268	9.3	72	5.6
Grade 4	1293	36.3	1121	23.6	733	12.7	409	6.6	118	4.2
Without irradiation:										
Grade 1	3	100.0	3	100.0	3	66.7	3	66.7	3	33.3
Grade 2	46	76.1	46	58.7	43	34.9	39	30.8	33	24.2
Grade 3	209	45.5	207	26.1	180	12.8	154	7.8	135	3.7
Grade 4	389	28.5	376	18.4	330	10.9	280	8.2	243	5.8
Concerning 409 patients treated with irradiation and 284 without irradiation†										
With irradiation:										
Grade 1	66	98.5	54	100.0	29	89.7	10	70.0	6	66.7
Grade 2	162	92.0	126	87.3	58	56.9	9	33.3	2	0
Grade 3	244	85.2	180	73.3	76	44.7	21	28.6	6	0
Grade 4	133	76.7	97	62.9	47	44.7	13	15.4	4	25.0
Without irradiation:										
Grade 1	83	94.0	62	88.7	32	78.1	25	64.0	20	60.0
Grade 2	124	86.3	109	76.1	63	58.7	38	36.8	34	26.5
Grade 3	120	74.2	115	56.5	80	42.5	58	37.9	57	31.6
Grade 4	104	60.6	101	53.5	89	39.3	69	29.0	67	22.4

*Only patients operated upon and traced for the different periods are included in this table.
†Grade of malignancy was not stated.

ninety-three cases of patients with carcinoma of the breast to determine the value of x-ray therapy. They used postoperative x-ray therapy in forty-one cases. Comparing the percentages of five-year survivals in the cases where there were no axillary metastases, they found a difference of 2 per cent, namely, 89 per cent five-year survivals, when postoperative x-ray therapy was used and 87 per cent when it was not used. This difference is certainly not significant, yet they state, "It is our opinion that operation combined with irradiation will practically double the results as compared with operation alone."

Schreiner[20] reviewed 283 cases of carcinoma of the breast. In 46 patients without axillary metastases and treated with irradiation therapy after a radical mastectomy, 65 per cent were classified as five-year survivals. When axillary metastases were present the five-year survivals fell to 23 per cent.

Evans and Leucutia[7] report 50 per cent five-year survivals in the group including patients with and without axillary metastases who had had a radical mastectomy, followed by x-ray therapy. They concluded that "irradiation therapy plays a paramount role in the treatment of mammary carcinoma both as an adjunct to surgery in the operable and as a primary method in the inoperable cases."

Harrington[11] divided 4,504 cases into those with patients with and without axillary metastases and then subdivided the groups into those with and without x-ray therapy and according to the four grades of the tumor, pathologically. This study led to very interesting results inasmuch as the follow-up was conducted over a period of twenty years. Harrington concluded "that irradiation therapy has not been any great adjunct to radical surgical treatment but may be of benefit in cases of higher grades of malignancy." (Table X.)

Shore[21] reported the follow-up of 375 cases in a series of 418 patients who had had a radical mastectomy. One-hundred and ninety-six were given routine postoperative prophylactic x-ray treatment; of these, 36 developed local recurrences (18.3 per cent). He does not state the percentage of these that had axillary metastases. The greatest number of recurrences in another table, however, was found in the patients with axillary metastases, regardless of x-ray therapy. His conclusions were that "postoperative irradiation rarely cures and usually does not prevent local recurrences and therefore does not decrease the mortality from cancer of the breast. It does, however, undoubtedly prolong some lives so that a few patients who would otherwise have died within five years after operations have survived several more months to be classified in the five-year group."

Adair[1] reports an interesting study of 2,467 operable cases.

"The conclusions from these statistics were that irradiation, either before or after the operations in cases with axillary involvement, had a decided value in this clinical group."

TABLE XI (FROM ADAIR)

471	had operation alone
857	had preoperative irradiation followed by radical surgery
485	had the radical mastectomy followed by irradiation
413	had irradiation alone
214	began treatment and then went elsewhere
27	had a local removal of cancer followed by irradiation therapy
2467	total

	Five-Year Results	
	NO AXILLARY INVOLVEMENT (%)	WITH AXILLARY INVOLVEMENT (%)
Operation alone	68	25
Preoperative irradiation followed by radical surgery	65	29
Radical surgery followed by postoperative irradiation	70	31
Irradiation alone	25	9

Brooks and Daniels[5] have reported an unusually high percentage of five-year survivals in a series of 72 radical mastectomies. They do not draw any conclusions, however, concerning irradiation therapy.

TABLE XII (BROOKS AND DANIELS)

	GROUP	CASE	LIVING AND WELL	PERCENTAGE
Given roentgenotherapy	I*	3	2	66.6
	II†	7	3	42.8
	III‡	9	1	11.1
Not given roentgenotherapy	I*	10	10	100.0
	II†	21	6	28.5
	III‡	22	3	13.6

*Carcinoma confined to breast.

†Carcinoma confined to breast and inferior axillary lymph nodes by microscopic study.

‡Carcinoma in breast and in axilla or near chest wall at operations.

SUMMARY AND CONCLUSIONS

1. A statistical study was made of 240 consecutive, unselected patients with mammary carcinoma who had radical mastectomies at the Henry Ford Hospital and of whom 234 have been accurately followed.

2. Chronic cystic mastitis was not present in a sufficient number of cases to imply any significant correlation between this pathologic process and cancer.

3. Carcinoma of the male breast occurred less frequently than in reports from other clinics.

4. The presence or absence of metastases at operation dominated all other clinical factors influencing prognosis.

5. Age did not appear to be an important factor per se.

6. A history of trauma occurred infrequently and a familial tendency to cancer did not occur frequently enough to seem significant.

7. The duration of symptoms before operation appeared to influence adversely the postoperative survival period.

8. Survival seemed to vary slightly with the quadrant of the breast affected.

9. The size of the tumor was not as important an indication of prognosis as was the presence or absence of axillary metastases.

10. Such a considerable error was found in the ability to detect and evaluate axillary nodes clinically that we believe palpation of the axilla should be discouraged as a diagnostic aid on account of the danger of massaging tumor cells out of involved glands.

11. Late lymphedema of the arm, tending to disappear after a time, was the most frequent form in which this complication occurred.

12. The postoperative mortality of 2.8 per cent in this series is discussed.

13. The five-year survivals of this series are discussed with particular reference to the presence or absence of axillary metastases and the use or nonuse of x-ray therapy.

14. X-ray therapy did not improve five-year survivals in those patients without axillary metastases. It seemed to add slightly to the survival of patients with axillary metastases.

15. The great value of x-ray therapy in the treatment of metastases, particularly those of bone, is stressed.

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THE PERITONEAL RESPONSE TO LOCALLY IMPLANTED CRYSTALLINE SULFONAMIDE COMPOUNDS*

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THERE is little need to recount the victories of the sulfonamide compounds in the field of surgery. The proper systemic use of these drugs has made deep inroads into the number of deaths attributable to infectious surgical complications: deaths that have plagued the most dexterous and conscientious surgeons. The local implantation of the sulfonamide compounds, in an attempt to exert their effects more fully, is an instance of medical empiricism now fully backed by clinical and laboratory confirmation. It is accepted generally that in high local concentration the bacteriostatic value of these drugs is enhanced. The metabolism of bacteria is altered, their growth is inhibited, their ability to form toxins and necrobiotic substances is impaired, and all this to the end that a mobilized cellular defense mechanism is able to overwhelm the attenuated organisms. It is conceded that the defense mechanisms of the body are necessary to the complete therapeutic activity of these drugs; however, the direct effect of local sulfonamide therapy on tissue defense has received little attention, although knowledge of possible relation between the two is essential to the rational employment of these drugs as local chemotherapeutic agents.

Most significant of these newer local applications has been the use of crystalline sulfonamide compounds within the peritoneal cavity. In this fashion the surgeon has been provided with a possible means of direct frontal attack on the problem of peritonitis. Clinical and experimental evidence of therapeutic efficacy has been accumulating; yet little actually is known of the peritoneal response to these substances. Therefore, it has been the purpose of this study to determine the peritoneal response to crystalline sulfonamide compounds, with special regard to their possible effects on the local peritoneal defense mechanism.

LITERATURE

Since the report of Dees, the topic of intraperitoneal sulfonamide therapy has received ever-increasing notice in the literature. Clinical reports have been followed closely by laboratory confirmation. The weight of favorable opinion has swept aside prejudice and inertia, and the value of intra-abdominal chemotherapy appears to be established in the minds of most physicians. However, the relation of this new weapon to the defensive forces of the peritoneal cavity has not been

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clarified. Hageman, studying the pathologic lesions of mice intoxicated with sulfanilamide, noted a mild fibroblastic foreign-body reaction about crystals of the drug, when it was administered intraperitoneally as a suspension in saline. Key and Frankel injected supersaturated solutions of sulfanilamide, sulfapyridine, and sulfamethylthiazole into body cavities and observed that the peritoneal surface presented little departure from normal. Jackson and Coller, using dogs, found that sulfanilamide administered intraperitoneally did not induce any cellular response in the peritoneal fluid. Small amounts of free fluid were noted, but no hyperemia or exudate was observed and the peritoneal surfaces appeared entirely normal. From these reports, it would seem that sulfanilamide, whether in solution or in crystalline form, produces little if any peritoneal reaction.

EXPERIMENTAL METHOD

The experimental animal chosen was the 100 Gm. albino rat. This choice was made because (1) the peritoneal responses of the white rat to various substances have been investigated intensively; (2) the peritoneal fluid of this animal normally has a high cellular content, and (3) the albino rat withstands laparotomy very well.

Peritoneal fluid was obtained in all instances by puncture with a clean, fine, glass capillary pipette. The fluid which entered the pipette by positive pressure was deposited on a clean glass slide and a sufficient amount was drawn into a hematologic white cell pipette for the total cell count. The remainder of the fluid was spread evenly over the slide for subsequent staining in order to determine the differential distribution of the cells. These air-dried films were stained with a May-Grünwald-Giemsa combination: thirty seconds in May-Grünwald stain, thirty seconds in equal parts May-Grünwald stain and Hayden's buffer at pH 6.4, and three to four minutes in buffer-diluted Giemsa stain, 1.5 drops to the milliliter of buffer.

The total and differential cell counts were recorded for the peritoneal fluid of each experimental animal prior to any experimental procedure. Following this, laparotomy was performed through a midline incision with the animal under ether anesthesia. One hundred milligrams of a powdered sulfonamide compound was distributed evenly about the peritoneal cavity and immediate suture was done with fine silk. In one group of rats, simple laparotomy was performed without the intraperitoneal implantation of any of the sulfonamide compounds. These animals constituted the control series. Total and differential cell counts were made on the peritoneal fluid of all animals on which operation was performed. The cell counts were made at twenty-four-hour intervals for periods ranging from five to seven days. Animals were killed at intervals by light etherization and exsanguination for pathologic study.

Estimations of the total quantity of peritoneal fluid were made by absorbing all free fluid into previously weighed pieces of filter paper. Increases of the weights of the filter paper were determined and accepted as weight of fluid.

The following drugs were implanted intraperitoneally in doses of 1 Gm. per kilogram of body weight: sulfanilamide, sulfathiazole, sulfapyridine, sulfadiazine, sulfamethyldiazine and sulfanilylguanidine.

RESULTS

Throughout the entire period of the experiment, no deaths occurred and no toxic manifestations were noted.

As may be seen (Table I) the mononuclear cells are the predominant cellular elements in the peritoneal fluid of the white rat. These have been divided empirically in this study, the nonphagocytic lymphocytes being placed in one group and the potentially phagocytic and usually larger mononuclear cells in the other. This latter group, referred to hereafter as mononuclear phagocytes, contains the typical monocytes and the true clasmatocytes as well as the various transitional forms. Differentiation of these mononuclear phagocytes was not attempted. It is notable that neutrophiles were not found in the normal peritoneal fluids; these cells, when present, are certain indications of a past or present pathologic condition. The eosinophilic leucocytes are subject to rather wide and inexplicable variations, while the mast cells almost disappear in the face of peritoneal irritation, a fact intensively investigated by Webb.

TABLE I

THE PERITONEAL FLUID OF THE NORMAL 100 GM. WHITE RAT MEAN VALUES OF FORTY-EIGHT ANIMALS

Total cells per cubic millimeter: 39,300
1. Mononuclear leucocytes: 71 per cent of total cell count
a. Large mononuclears (phagocytes): 70 per cent of all mononuclear cells
b. Lymphocytes: 30 per cent of all mononuclear cells
2. Eosinophiles: 23 per cent of total cell count
3. Mast cells (basophiles): 6 per cent of total cell count
4. Neutrophiles: 0
Weight of peritoneal fluid: 285 mg. (six determinations)

Throughout the period of the experiment, certain abnormalities were encountered in the cytologic characteristics of the peritoneal fluid of approximately 30 per cent of the animals used. Such animals, though usually healthy in other respects, were not included in the compilation of these data. The apparent reasons for these variations from the normal were (1) dehydration; (2) peritoneal infection, usually the result of visceral puncture, and (3) endemic enteritis.

Control Group: Peritoneal Response to Simple Laparotomy.—This group comprises sixteen animals and a brief of the important data is shown in Table II. As noted previously by Higgins and Montgomery, simple laparotomy, when carefully performed, causes little actual change in the cytologic picture of the peritoneal fluid. Most striking is the influx of neutrophiles (Fig. 1), a fact which is mirrored in the transient increase of the total cells per cubic millimeter of fluid. The mononuclear cells at first glance seem to undergo a decrease but further analysis shows that this diminution of mononuclears (as well as eosinophiles) is only relative to the influx of neutrophiles. The inclusion of the neutrophile in any differential study merely adds an extrinsic variable which distorts the true ratio of the cells normally found in the peritoneal fluid, a fact appreciated by Webb in his statistical analysis. The term, "relative differential count," has been used in this

report for differential data calculated without inclusion of neutrophiles. This method of calculation gives, it would seem, a truer picture of cellular relation in the peritoneal fluid than does the differential count in

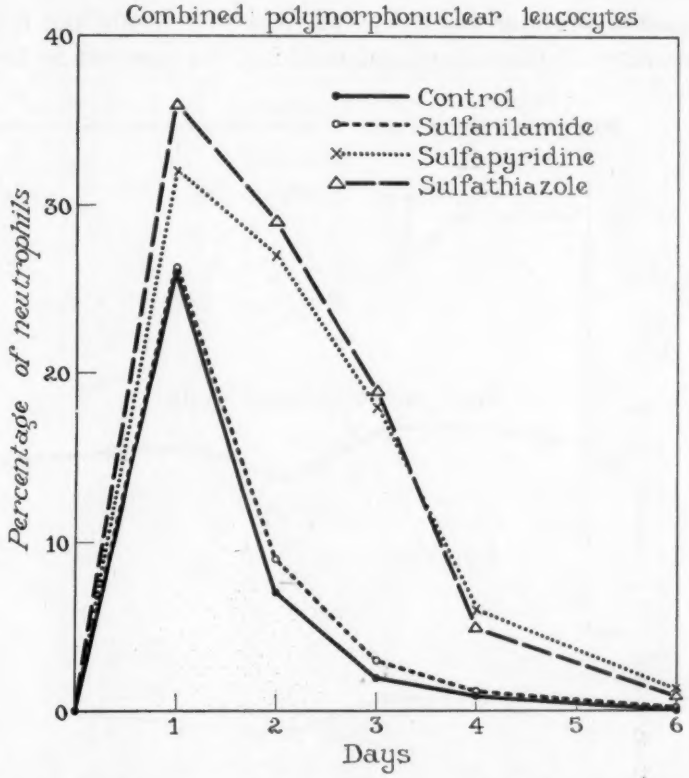

Fig. 1.—Percentage distribution of the neutrophiles of the peritoneal fluid following laparotomy and the implantation of certain sulfonamide compounds.

TABLE II

PERITONEAL RESPONSE TO LAPAROTOMY

MEAN VALUES OF SIXTEEN ANIMALS

HOURS AFTER OPERATION	TOTAL CELL COUNT PER CUBIC MILLIMETER OF PERITONEAL FLUID	DIFFERENTIAL CELL COUNTS							
		ACTUAL				RELATIVE			
		NEUTROPHILES	MONOCYTES	EOSINOPHILES	MAST CELLS	MONOCYTES	EOSINOPHILES	MAST CELLS	LYMPHOCYTE PHAGOCYTE RATIO
Control	39,300	0	71	23	6	71	23	6	23:77
24	83,800	26	53	19	2	72	25	3	22:78
48	59,000	7	69	23	1	72	26	2	22:78
72	57,600	2	67	28	3	69	28	3	22:78
120	55,200	1	70	26	3	71	26	3	23:77
168	61,300	0	70	28	2	70	28	2	

which neutrophiles are included. Thus, it is apparent that the relative numbers of mononuclear cells and eosinophiles are unchanged by laparotomy and the ratio of mononuclear phagocytic elements to lymphocytes remains unaltered (Fig. 2).

The Response Within the Peritoneal Cavity to Sulfanilamide.—Twelve animals were used in this series. Although the amounts of sulfanilamide were rather large, gross evidence of the drug was not visible six to eight hours after its introduction into the peritoneal space. There was no hyperemia of either visceral or parietal peritoneum and a transitory initial increase of the quantity of fluid had disappeared in twenty-four

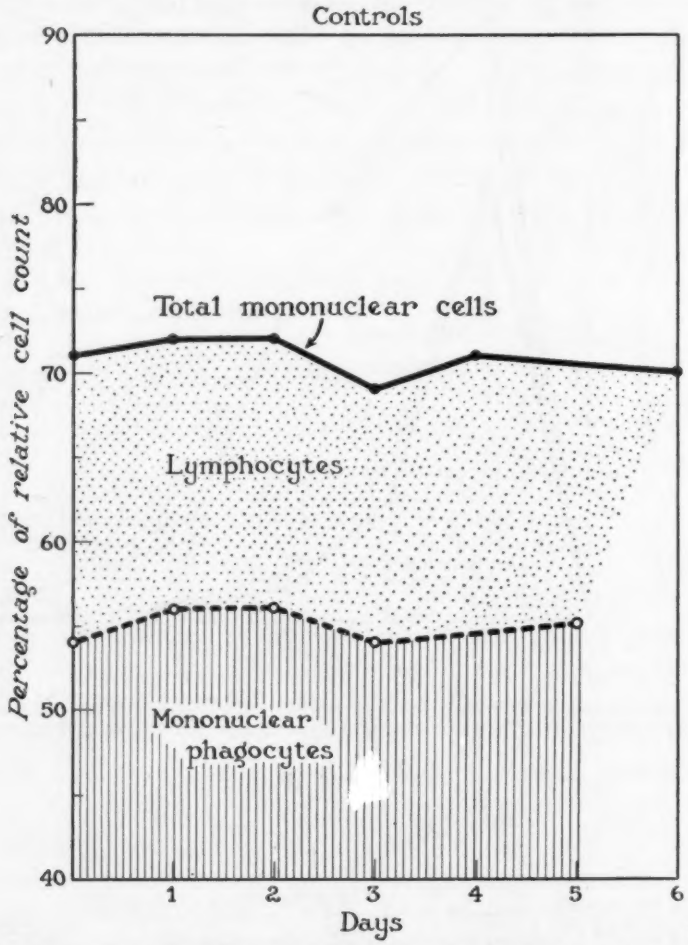

Fig. 2.—Percentage of mononuclear components of the total number of cells, exclusive of neutrophiles, following laparotomy.

hours. The cellular reaction to sulfanilamide had two important characteristics: (1) The neutrophile response was not beyond levels observed in control animals (Fig. 1). Thus, it appears that sulfanilamide when introduced intraperitoneally does not induce any acute inflammatory response. (2) There did occur, however, a low-grade stimulation of the large mononuclear phagocytic cells, together with a gradual increase of 10 per cent in their number over a six-day period (Fig. 3). This reaction is typical of extremely mild peritoneal irritation. At post-mortem examination, seven to fourteen days after the introduction

of sulfanilamide, the only observations of importance were a lack of adhesions, except as in the control series, and some enlargement of the spleen. This organ, which was almost black, confirmed previous observations of Machella and Higgins, and showed neither microscopic changes nor increased iron deposits.

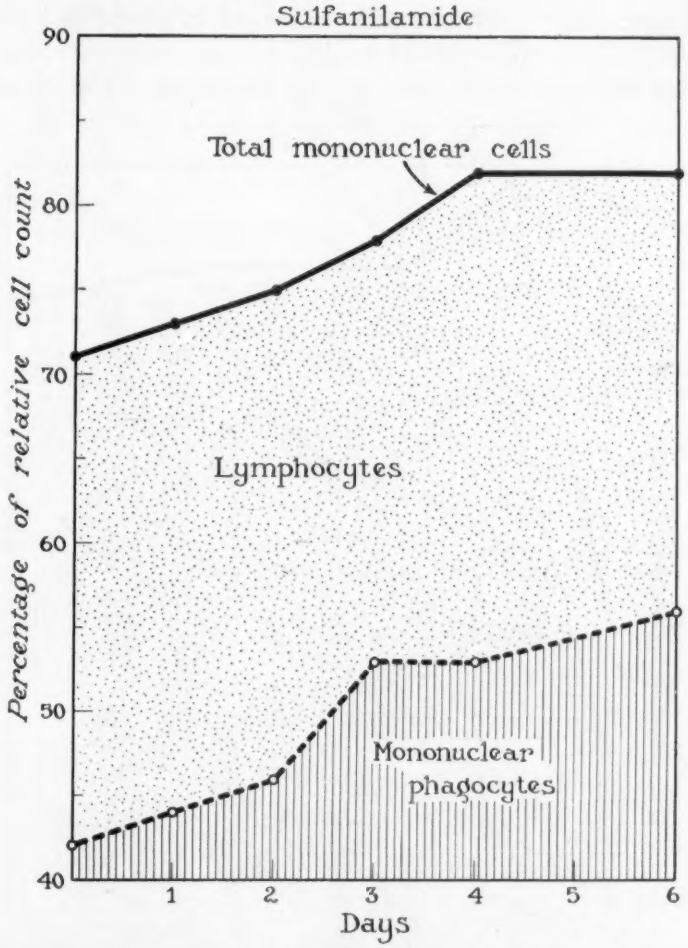

Fig. 3.—Percentage of mononuclear components of the total number of cells, exclusive of neutrophiles, following the intraperitoneal implantation of sulfanilamide.

The Response Within the Peritoneal Cavity to Sulfathiazole.—Eighteen animals were used in this series. Sulfathiazole remained grossly visible for three to five days. During the first forty-eight hours, the drug generally appeared as agglutinated masses, floating freely and not evidencing any tendency to serosal attachment or peritoneal damage. Any undissolved clumps of the drug were taken up subsequently by the omentum and had dissolved completely therein by the third to fifth day. In this connection, several features are of note. First, the more uniform the implantation of the drug about the peritoneum, the less likely are undissolved clumps of the drug to remain for subsequent omental disposal. Second, the use of crystals instead of the powdered

drug greatly facilitated the implantation, because the powder tends to mass itself in damp clumps, like confectioners' sugar, while the crystalline form distributes itself more evenly like granulated sugar. In either instance, the peritoneal cellular response was identical. This reaction was characterized by (1) minimal serosal damage, as evidenced by lack of adhesions; (2) a moderate and prolonged neutrophilic response, as compared with control levels (Fig. 1); (3) an immediate and marked increase of the number of mononuclear phagocytes (Fig. 4), in which

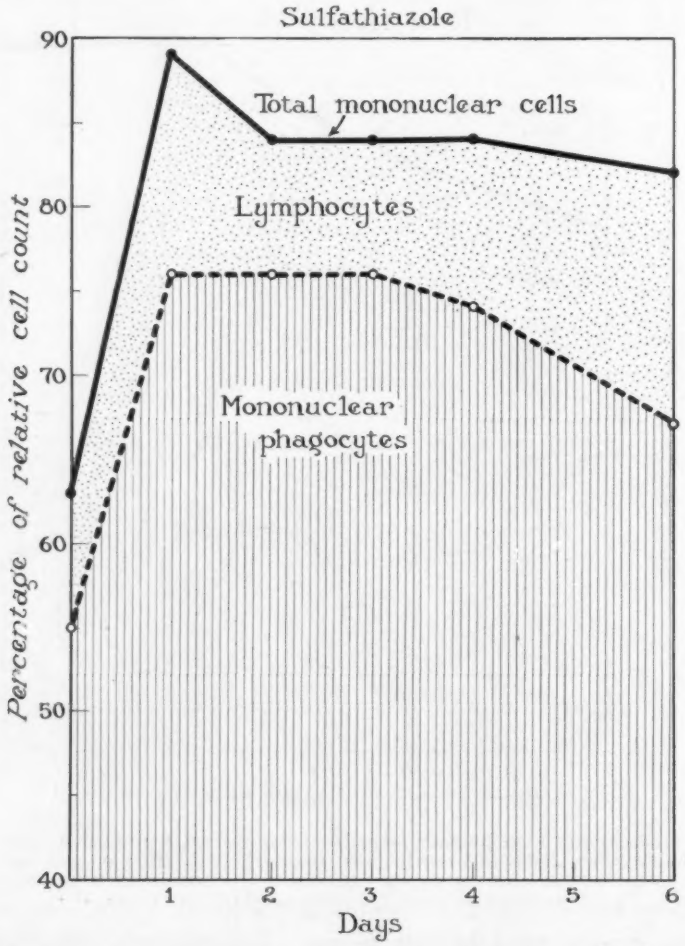

Fig. 4.—Percentage of mononuclear components of the total number of cells, exclusive of neutrophiles, following the intraperitoneal implantation of sulfathiazole.

there was evidence of extreme activity (large size, multinucleation, cytoplasmic inclusions and vacuolization, and rare mitotic figures), and (4) a noticeable increase of the total cell count per cubic millimeter of fluid beyond control levels. This not only reflects an actual cellular increment but also shows that the degree of peritoneal irritation had not been severe enough to produce a fluid dilution factor. This latter observation was borne out by actual measurement.

At necropsy, ten to fourteen days after the introduction of sulfathiazole, the peritoneal cavities were essentially normal. There were no notable adhesions, although a very occasional focus of milky fibroblastic proliferation occurred in regions where a mass of the drug had dissolved slowly in contact with the liver. The spleens were moderately black and enlarged in about 75 per cent of the animals, recalling the condition previously described in all the animals receiving sulfanilamide.

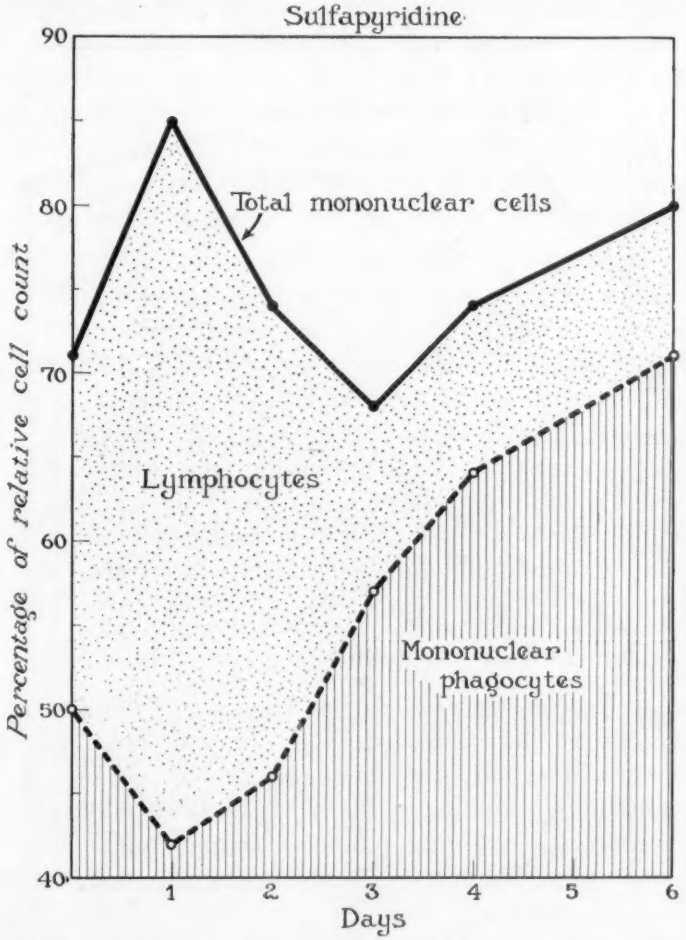

Fig. 5.—Percentage of mononuclear components of the total number of cells, exclusive of neutrophiles, following the intraperitoneal implantation of sulfapyridine.

The Response Within the Peritoneal Cavity to Sulfapyridine.—Twenty animals were used in this series. In these experiments sulfapyridine proved to be a strong peritoneal irritant. As late as twenty-four hours after its introduction into the peritoneal cavity, the actual quantity of peritoneal fluid recovered was 470 mg. as compared with 215 mg. for controls on which operation had been performed. Furthermore, the agglutinated masses of drug were sufficiently irritating to produce serosal attachment. These clumps of drug were walled off rapidly

among the viscera and by the omentum, and frequently could be seen, fourteen days after implantation, surrounded by foreign-body giant cells. Organizing adhesions were frequent and one instance of partial intestinal obstruction was noted. The cellular reaction was characterized by (1) a response of the neutrophiles similar to that induced by sulfathiazole (Fig. 1); (2) an initial shower of lymphocytes, the small round cells of inflammation, followed by a rapid accumulation of mononuclear phagocytic cells (Fig. 5), phenomena which are indicative of

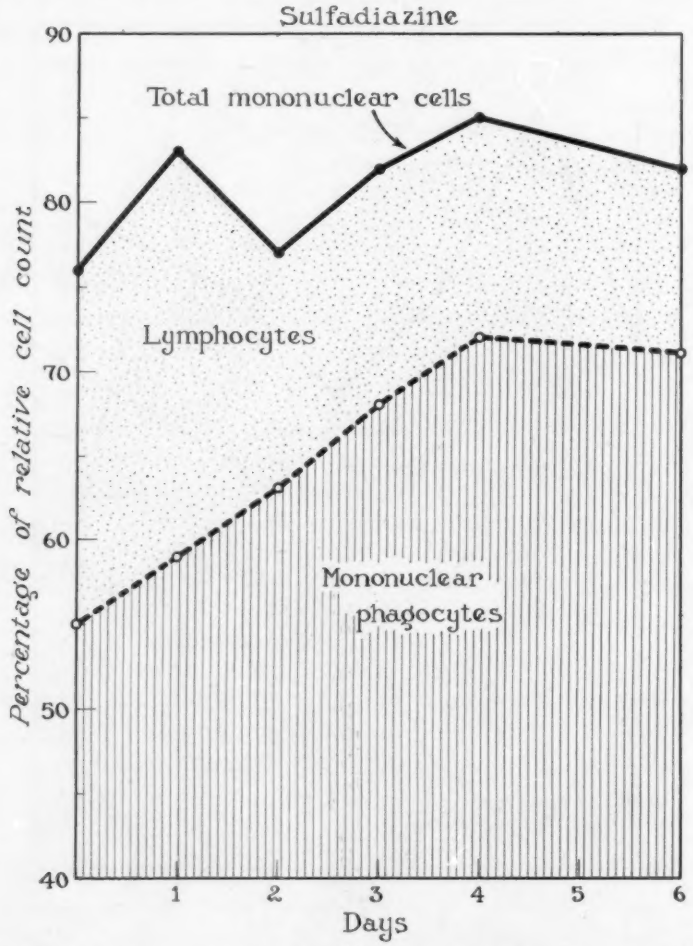

Fig. 6.—Percentage of mononuclear components of the total number of cells, exclusive of neutrophiles, following the intraperitoneal implantation of sulfadiazine.

violent peritoneal irritation, as seen in aleuronat peritonitis or following intraperitoneal injection of sodium ricinoleate, and (3) an inflammatory increase of the peritoneal fluid sufficient to cause a noticeable dilution factor in the total cell count per cubic millimeter. At necropsy, the spleens were not notably enlarged but were dark in about 50 per cent of the animals.

The Response Within the Peritoneal Cavity to Sulfadiazine.—This drug was used in a series of six animals and found to be only slightly

less irritating than sulfapyridine. At twenty-four hours after implantation, masses of sulfadiazine were firmly adherent to adjacent tissue surfaces, lying between the incision and the omentum. However, by the sixth postoperative day, only an occasional remnant of the drug remained undissolved.

The peritoneal reaction to sulfadiazine was characterized by (1) some serosal attachment and damage; (2) a walling off of the agglutinated masses of the drug, to a lesser degree than that produced by sulfapyridine; (3) a noticeable neutrophilic leucocytic reaction; (4) a small initial shower of lymphocytes, together with a rapid and steady increase of the large mononuclear phagocytic cells (Fig. 6), and (5) an inflammatory increase of the quantity of peritoneal fluid to 330 mg. in twenty-four hours, sufficient to produce a notable dilution of the total cells per cubic millimeter. The spleens were normal in all animals.

The Response Within the Peritoneal Cavity to Sulfamethyldiazine and Sulfanilylguanidine.—These drugs were used in small series, six animals for sulfamethyldiazine and twelve for sulfanilylguanidine. The gross peritoneal responses to them were almost identical and somewhat similar to that elicited by sulfathiazole. The drugs evidenced little tendency to serosal damage or attachment, grossly disappeared from the peritoneum in three to five days, and produced cellular responses somewhat like those elicited by sulfadiazine. The spleens were not affected by sulfamethyldiazine, but in approximately 30 per cent of animals receiving sulfanilylguanidine the previously described splenic changes were observed at necropsy.

COMMENT

The sulfonamide compounds are bacteriostatic drugs; their action in the body is to prevent invasion. The summation of their effect is simply an attenuation of virulent microorganisms, holding them in check until the local tissue defenses, long ago perfected by nature, can overwhelm them. Thus, in the final analysis, it is the mustering defensive forces of the body which repel the invader and repair the damage, a fact appreciated by Paracelsus, in 1536. With this in mind, it must be apparent that intraperitoneal sulfonamide therapy is a valuable adjunct to abdominal surgery, but its use does not lessen the responsibilities of the surgeon. Among these responsibilities is the choice of the proper sulfonamide compound for intraperitoneal implantation. Should one postulate an ideal sulfonamide compound for intraperitoneal use, it is certain that the following qualities would be included: (1) The compound should be active against a variety of microorganisms; (2) it should be innocuous to the peritoneum; (3) it should exert a prolonged bacteriostatic effect; (4) it should stimulate the natural local defense mechanism, to complement the attenuating effect of the drug on the invading bacteria.

With these four premises in mind, it is apparent from these experimental data that sulfathiazole, of the sulfonamide compounds now in general use, is the most logical choice. It is bacteriostatic against most of the commonly encountered pyogenic microorganisms, and especially against *Streptococcus faecalis* and *Escherichia coli*, those symbiotic invaders so common in peritonitis. It is innocuous to the peritoneum and contiguous structures. It exerts a prolonged action, remaining grossly visible and unattached in the peritoneum for three or four days. Some clinical proof of this lies in a statement by Herrell that levels of this drug of more than 500 mg. per 100 c.c. are maintained readily in the human peritoneal exudate for four to five days following its implantation in quantities of 10 Gm. And lastly, sulfathiazole musters the local defensive forces to an effort that equals any produced by the usual means of intraperitoneal vaccination.

This latter reaction deserves some attention. The cellular responses elicited by the sulfonamide compounds when implanted intraperitoneally are qualitatively those of nonspecific peritoneal irritation. The quantitative differences observed evidently are allied to such factors as solubility and chemical irritation rather than to any possible specific cellular stimulation. The peritoneal response produced by the rapidly dissolving and inert sulfanilamide is meager at best. At the other extreme, the response initiated by the irritating sulfapyridine is so violent that the masses of drug are walled off from the general peritoneal cavity long before their solution is complete. Midway between these two is the peritoneal response to sulfathiazole. This drug seems to act as a slowly dissolving, nonirritating foreign body. Not only does the cellular reaction provide neutrophiles as a first line of defense, but, more important, there is a rapid augmentation of mononuclear phagocytes, the real bulwark of cellular defense and the potential building units of reparative processes. Regardless of such factors as omental migration, fluid dilution, and antibody reaction, the mononuclear phagocyte is probably the most important single element in the peritoneal defense. This response to sulfathiazole is the equal of that inspired by methods of peritoneal vaccination, as studied in the rat by Seely, Higgins, and Mann.

The sulfonamide compounds, in local application, offer a means of attack on peritoneal infection, not only therapeutically but also prophylactically. The ability of sulfathiazole to enhance the local cytologic defense mechanism, in conjunction with prolonged bacteriostasis, would seem to make it the sulfonamide compound of choice for intraperitoneal use. This theoretical superiority is being borne out and confirmed by recent studies, especially the controlled experiments on peritonitis of animals by Epps, Ley, and Howard.

No reasonable explanation for the discoloration of the spleen is at hand. Some investigations by Machella and Higgins, and by Feldman,

Hinshaw and Moses suggest that pigmentation with a sulfhemoglobin compound may be the answer.

SUMMARY

An experimental technique is reviewed for the study of the peritoneal responses to crystalline sulfonamide compounds. Data are presented on the peritoneal responses of the white rat to simple laparotomy and the intraperitoneal implantation of sulfanilamide, sulfathiazole, sulfapyridine, sulfadiazine, sulfamethyldiazine, and sulfanilylguanidine. Each of these drugs produces some peritoneal reaction, as mirrored in the cellular changes which take place in the peritoneal fluid. These reactions, ranging from the meager response to sulfanilamide to the violent responses induced by sulfapyridine, are nonspecific and depend on a foreign-body reaction of the tissues toward the drug itself, as well as on the innate irritant properties of certain of these compounds. The relation of this local tissue response to the efficacy of sulfonamide therapy is stressed. These drugs owe their therapeutic value to properties of bacteriostasis; the actual killing and disposal of the attenuated bacteria are performed by the local cellular defense mechanism. The augmentation of the peritoneal cellular defenses by these drugs in local application is of great value, complementing as it does their bacteriostatic properties. However, the vigorous response initiated by certain of the sulfonamide compounds, especially sulfapyridine, walls them off from the general peritoneal cavity so rapidly as to reduce their effectiveness as bacteriostatic agents. Of the sulfonamide compounds used in this study, it would seem that sulfathiazole has certain advantages as an intraperitoneal chemotherapeutic agent: (1) it is active against a variety of microorganisms; (2) it is innocuous to the peritoneum; (3) it exerts a prolonged bacteriostatic effect, and (4) it stimulates the local cytologic defense mechanism to an effort the equal of any inspired by usual methods of peritoneal vaccination.

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COMPARATIVE BLOOD CONCENTRATIONS OF SULFAGUANIDINE, SULFANILAMIDE, AND SULFATHIAZOLE AFTER ADMINISTRATION ORALLY, PERITONEALLY, AND PLEURALLY TO DOGS

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INTRODUCTION

THE relative rates of absorption of sulfanilamide and sulfathiazole from the gastrointestinal tract, peritoneal cavity, and pleural cavity of dogs have been previously reported from the laboratory of the Medical College of Virginia with a brief discussion of the clinical significance of such observations.[1, 2] Since the introduction of sulfaguanidine,[3] studies have been made as to its bacteriostatic effect on intrapleural application[4]; its local effects on the peritoneal cavity[5]; and its diffusing tendency when placed in wounds.[6] The fact that sulfaguanidine was regarded as being especially poorly absorbed from the gastrointestinal tract, had a low systemic toxicity, and had been found to be effective against several types of pathogenic organisms,[3] would suggest that its use peritoneally and pleurally might provide an unusually safe local bacteriostatic measure of relatively prolonged effectiveness. For these several reasons it was thought of some interest and possibly of some importance to duplicate the earlier experiments on sulfanilamide and sulfathiazole using sulfaguanidine, and to compare the results of such tests with those obtained with the two former compounds.

EXPERIMENTAL

Mongrel dogs of mixed sexes and weighing 8 to 15 kg. were used as experimental subjects. Prior to experimentation they were deprived of food for about twelve hours, and after administration of the drug, both food and water were withheld for six or seven hours. For the purpose of determining the extent of sulfaguanidine absorption, samples of blood were taken from the saphenous vein at hourly intervals for the first six or seven hours after medication, and then, finally, after twenty-four hours. A sample for control was also taken immediately before experimentation. The blood concentration of sulfaguanidine was determined by a modification of the method described for sulfanilamide by Bratton and Marshall,[7] using a photoelectric colorimeter with filter No. 540.

When the sulfaguanidine was given orally, it was administered, suspended in water, by means of a stomach tube. For intrapleural and intraperitoneal administration, aseptic surgical procedures were followed, the animal being anesthetized with ether without premedication.

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The incisions were closed with catgut and silk, and the animals allowed to recover. When the drug was administered into the pleural space, a long incision was made into the fourth right interspace and the powdered sulfaguanidine dusted on the visceral pleura. For intraperitoneal dosage a midline incision was made between the symphysis pubis and the xyphoid of the sternum, the drug being applied to the intestines directly under the greater omentum.

RESULTS

Fig. 1 illustrates the results of our observations when the dose of sulfaguanidine for each of the three methods of administration was 100 mg. per kilogram of body weight, four dogs being used for each method

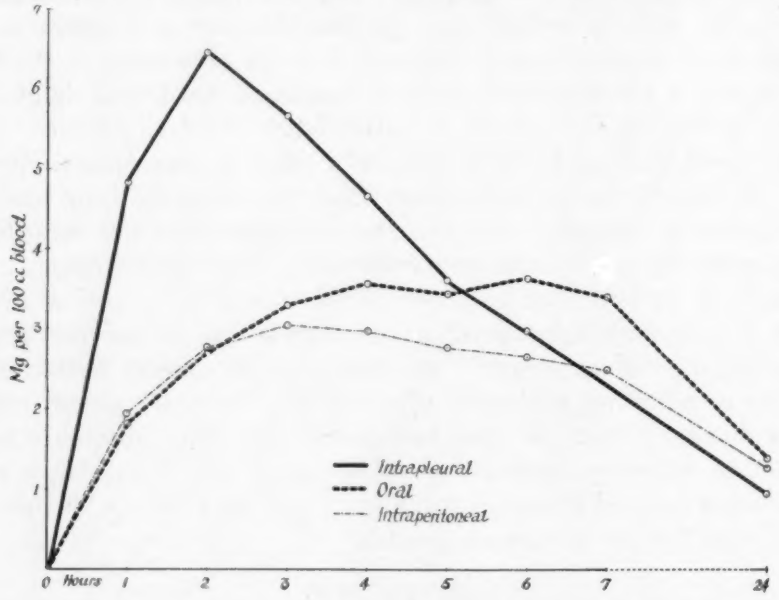

Fig. 1.—Comparative absorption rate of sulfaguanidine in dogs following various routes of administration. Dose of sulfaguanidine, 100 mg. per kilogram.

and the blood concentration values averaged. This is the dose of sulfaguanidine which has been used by oral administration in man.[8] Table I

TABLE I

T VALUES FOR THE DIFFERENCES IN THE BLOOD CONCENTRATIONS OF SULFAGUANIDINE FOLLOWING DIFFERENT METHODS OF ADMINISTRATION IN DOGS (SIX DEGREES OF FREEDOM THROUGHOUT)

TIME (IN HOURS)	ORALLY/PERITONEALLY	ORALLY/PLEURALLY	PLEURALLY/PERITONEALLY
1	0.43	6.26	6.41
2	0.23	6.26	6.59
3	1.00	3.61	4.00
4	1.90	1.50	5.21
5	1.96	0.07	0.95
6	2.48	1.48	0.66
7	2.53	----	----
24	0.76	2.76	1.70

T values at the 5 per cent point should be 2.447, at the 1 per cent point, 3.707. For direction of curves refer to Fig. 1.

indicates the statistical significance[9] of the differences between the rate of absorption from the several surfaces, the least significant differences being noted on comparison of absorption following oral administration with that following peritoneal administration. The values for the blood concentrations after administration orally coincide with those obtained by Marshall, Bratton, White, and Litchfield.[3]

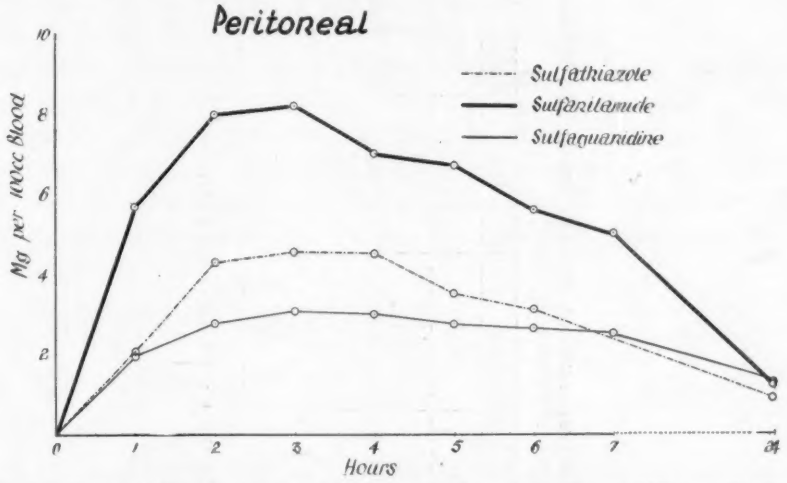

Fig. 2.—Comparative average blood concentrations of sulfaguanidine, sulfanilamide, and sulfathiazole in dogs after peritoneal administration. Five dogs were used for the sulfanilamide, four for the other compounds; the dose of each was 100 mg. per kilogram.

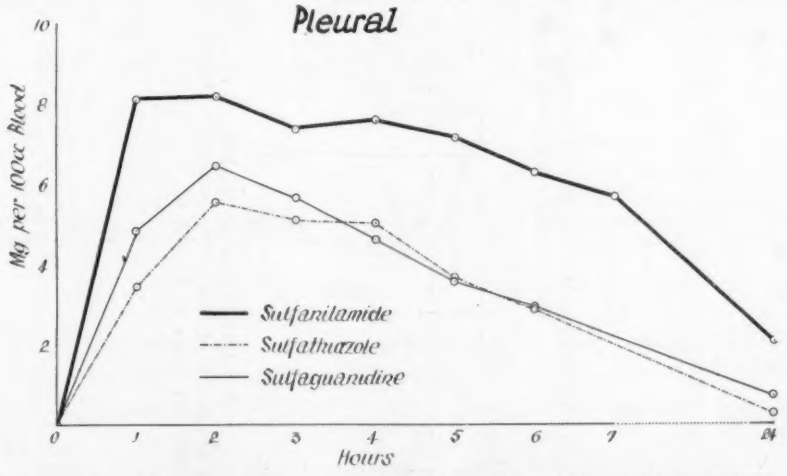

Fig. 3.—Comparative average blood concentrations of sulfaguanidine, sulfanilamide, and sulfathiazole in dogs after pleural administration. Four dogs were used for each compound; the dose of each was 100 mg. per kilogram.

Another small series of experiments was performed to determine approximately the relationship between dose and subsequent blood concentration of the drug. One dog received 200 mg. of sulfaguanidine per kilogram intraperitoneally; the peak blood concentration of 4.88 mg. per 100 c.c. was reached after five hours. Two other dogs similarly received 400 mg. per kilogram. Neither of these latter dogs showed so

TABLE II

T VALUES FOR THE DIFFERENCES IN THE BLOOD CONCENTRATIONS OF SULFAGUANIDINE, SULFANILAMIDE, AND SULFATHIAZOLE FOLLOWING DIFFERENT METHODS OF ADMINISTRATION IN DOGS*

TIME (IN HOURS)	SULFANILAMIDE/SULFAGUANIDINE			SULFANILAMIDE/SULFATHIAZOLE			SULFATHIAZOLE/SULFAGUANIDINE		
	PERITONEALLY*	PLEURALLY	ORALLY	PERITONEALLY*	PLEURALLY	ORALLY	PERITONEALLY	PLEURALLY	ORALLY
1	4.98	1.74	5.96	4.06	2.52	4.36	0.18	3.27	1.10
2	9.28	2.82	11.00	2.79	4.28	10.00	1.82	1.14	1.43
3	7.32	1.52	12.85	3.34	2.27	3.55	1.98	0.58	1.28
4	4.73	3.59	14.23	2.33	4.81	5.56	1.97	0.61	0.43
5	5.00	4.90	12.90	3.52	4.68	4.68	1.32	0.35	0.58
6	3.97	7.67	4.71	2.85	6.59	2.83	1.21	0.18	0.18
7	3.62	---	3.62	---	---	---	---	---	---
24	0.14	3.08	0.65	0.61	4.42	1.50	1.08	2.64	6.00

*Six degrees of freedom throughout except as asterisked (seven degrees).
T values (six degrees of freedom) at the 5 per cent point should be 2.447; at the 1 per cent point, 3.707.
For direction of curves refer to Figs. 2, 3, and 4.

high a blood concentration as the first one, except after twenty-four hours, when the average blood concentration of these two (2.85 mg. per 100 c.c.) was twice that of the first (1.41 mg. per 100 c.c.). Another dog was given 400 mg. per kilogram orally; the blood concentration of sulfaguanidine never reached the levels noted in the animals receiving only 100 mg. per kilogram. These observations are in keeping with those of Marshall and his associates[3] on mice and dogs.

Figs. 2, 3, and 4 show the comparative blood concentrations of sulfanilamide, sulfathiazole, and sulfaguanidine after their administration in identical amounts peritoneally, pleurally, and orally. The values of sulfanilamide and sulfathiazole are those obtained in earlier studies,[1, 2] performed in a similar fashion as the present ones, with sulfaguanidine. Table II gives the statistical significance of the differences found between the blood levels of the various drugs on administration by the several methods.

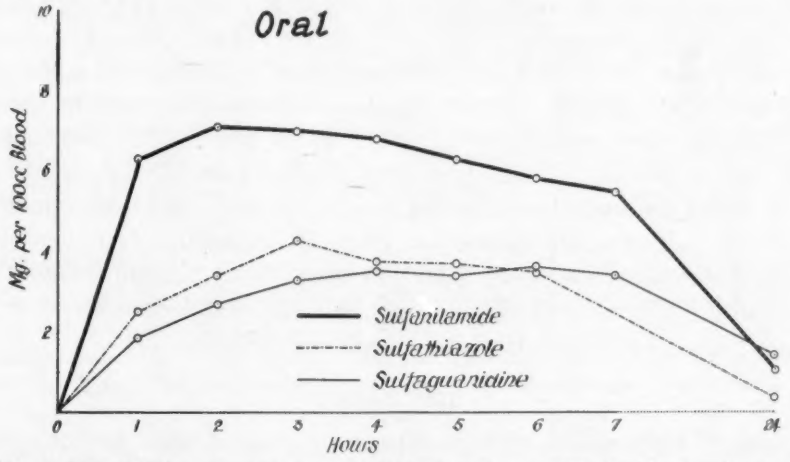

Fig. 4.—Comparative average blood concentrations of sulfaguanidine, sulfanilamide, and sulfathiazole in dogs after oral administration. Four dogs were used for each compound; the dose of each was 100 mg. per kilogram.

DISCUSSION

While sulfaguanidine has been considered as being poorly absorbed from the gastrointestinal tract, the first report on the compound by Marshall and co-workers[3] showed that after administration in doses of 100 mg. per kilogram orally to dogs, from 60 to 70 per cent of the chemical could be accounted for in the urine within twenty-four hours; this indicates a degree of absorption and elimination approximately that of sulfathiazole.[10] Low blood concentration values in the case of any drug need not necessarily mean poor absorption, but actually might mean good absorption with rapid elimination. This is what apparently occurs with sulfaguanidine.[11] Marshall and his colleagues[3] found in dogs that doses of sulfaguanidine larger than 100 mg. per kilogram produced lower blood and urinary excretion levels. We have had similar experiences. Corwin[12] observed that after oral administration to monkeys of sulfa-

nilamide, sulfathiazole, and sulfaguanidine in doses of 400 mg. per kilogram, sulfaguanidine gave the lowest blood concentrations with sulfathiazole next, and then sulfanilamide. This dose of sulfaguanidine is probably not one to show optimal absorption from the gastrointestinal tract.

Our experiments coincide with more recent experiences that have shown that sulfaguanidine may be rather well absorbed from the gastrointestinal tract.[11] The fact that sulfaguanidine is, as a rule, as rapidly absorbed from the gastrointestinal tract, pleural cavity, and peritoneal cavity is in keeping with our previous results obtained with sulfanilamide and sulfathiazole.[1, 2] The present experiments also suggest that the persistence of bacteriostatic action would be no greater with this substance than with sulfathiazole.

CONCLUSIONS

In normal dogs the rates of absorption of sulfaguanidine in a dose of 100 mg. per kilogram body weight are nearly equal from the gastrointestinal tract and the peritoneal cavity. Absorption from the pleural cavity is definitely more rapid than from either of the other two sites during the first three or four hours after administration.

In similar dosage, sulfanilamide produces generally a significantly higher blood concentration after peritoneal, pleural, and oral administration than either sulfaguanidine or sulfathiazole. The two latter sulfonamides produce more nearly equal blood concentrations. Experimental evidence does not indicate that sulfaguanidine would exhibit a more lasting local bacteriostatic effect than sulfathiazole.

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DRAINAGE OF THE EXTERIORIZED LIVER (EXTERNAL HEPATOSTOMY)

A Palliative Operation for Jaundice

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A WOMAN 68 years old, intensely jaundiced from carcinoma of the biliary tract, was transferred to Temple University Hospital, Nov. 30, 1940, in the hope of obtaining relief from the extreme itching and nausea. No local or general remedy had been palliative, and sedatives and narcotics gave the patient little rest.

Gallstones were removed and a cholecystogastrostomy was done under local anesthesia on Dec. 4, 1940. As the common bile duct seemed fused in a mass of malignant tissue and the gall bladder free from bile, it was not surprising that no improvement followed the operation. Twenty-six days later, under spinal anesthesia, the abdomen was opened again in the hope of finding some outlet for the bile. There were multiple 5 to 7 mm., firm, grayish, metastatic nodules in the liver. One of these was removed for microscopic study by a wedge-shaped resection of the free edge of the right lobe of the liver. Instantly, clear colorless bile poured from a minute duct on the incised surface. The edge of the right lobe, therefore, was exteriorized with four interrupted transfixion sutures of fine alloy steel wire, and the skin and deeper structures closed about the organ with layer interrupted wire sutures. A double suction drain of alloy steel was inserted through a stab wound beneath the liver to evacuate continuously any peritoneal liquids resulting from leakage or exudation. Petrolatum gauze was applied over the exposed liver. Bile, which soon became amber colored, ran from the 1 mm. opening. The jaundice soon cleared and the patient, relieved of the intolerable skin irritation and nausea, was enabled to sleep, to eat, to discontinue using narcotics, and later to leave her room. It was possible to pass a probe to the depth of about 12 cm. into the minute hepatic duct. When an attempt was made to dilate the duct for the insertion of a small cannula, the delicate wall ruptured. The patient returned to her home, January 19. A thin film of epithelium gradually spread over the exposed surface of the liver and the drainage finally ceased, with return of the jaundice and pruritus in March. The patient re-entered the hospital, March 12, 1941, and a thin slice or wedge of the exposed liver was removed painlessly without an anesthetic, opening new ducts. The oozing of blood soon ceased under gauze pressure and the patient was discharged relieved three days later. By April 28, epithelium again had spread over the liver surface and the abdomen had become markedly distended by fluid. A wedge of liver about 8 cm. long, 2 cm. wide, and 2 mm. deep was excised. This was followed immediately by a free flow of bile. Oozing was arrested by light gauze pressure, and a slender, double lumen suction drain for continuous aspiration was inserted into the abdomen under local anesthesia.

The patient died from the progress of the disease about five weeks later. At no time was there suppuration, inflammatory reaction, or

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evident malignant change of the exposed part of the liver, nor did the skin show irritation from contact with the escaping bile. Through the drainage of bile the progress of the disease became nearly painless and the patient, no longer requiring narcotics, also was relieved of the disturbances resulting from the use of such drugs.

Previous to the above experience, a baby 7 months old, jaundiced from birth and with a greatly enlarged liver, was admitted. Explora-

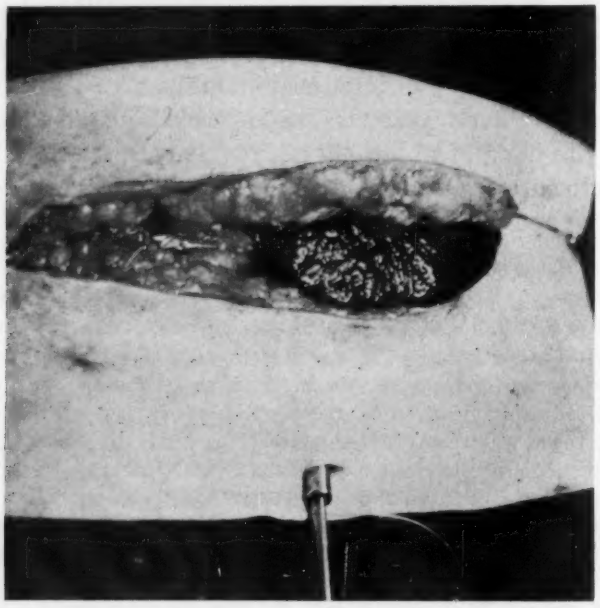

Fig. 1.—Liver exteriorized in the abdominal wound previous to suture.

Fig. 2.—Exteriorized liver, showing flow of bile two and one-half-months after external hepatostomy.

tory operation, Sept. 15, 1939, showed a large firm liver with very irregular surface. No evidence of gall bladder or of extrahepatic biliary ducts was detected and the condition of the child led me to close the abdomen without attempting to form an anastomotic channel between the liver and the gastrointestinal tract. Not until kodachrome

Fig. 3.—Jaundice and enlarged liver in 7-month-old baby, from agenesis of the extrahepatic biliary system.

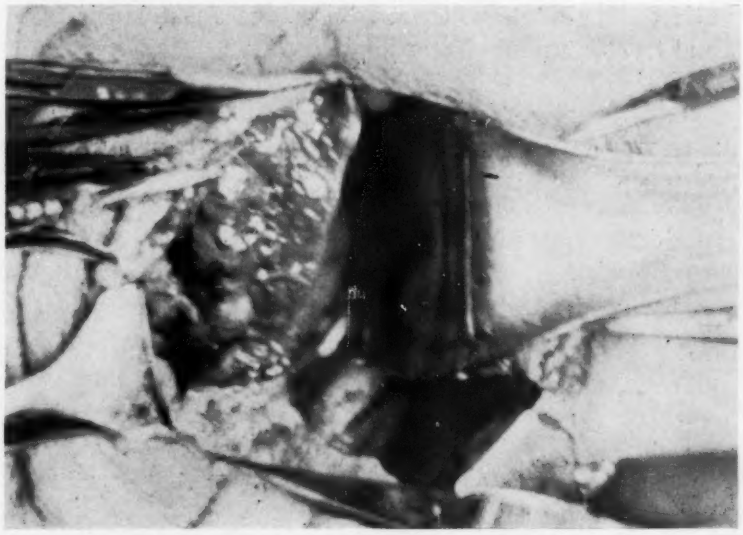

Fig. 4.—Enlarged liver with greatly dilated bile ducts, shown during operation on the baby.

pictures, taken during the operation, were thrown on a screen was it recognized that the liver surface was covered with greatly dilated bile ducts. In the meantime the child had been returned to his home in a distant town and had died from the progress of the disease. With the subsequent experience, I now, in such a case, would establish a biliary fistula from the surface of the liver in the hope of later anastomosing the fistula with the alimentary tract, either in the manner described previously[1] or in some other way.

SUMMARY

1. A case is presented in which the edge of the liver was exteriorized upon the surface of the abdomen for about five months without unfavorable reaction.

2. The exteriorized liver gradually became covered by a film of squamous epithelium derived from the adjacent skin.

3. From a minute duct opened on the edge of the liver, sufficient drainage of bile occurred to relieve the patient of jaundice and its distressing symptoms.

4. With closure by epithelization of open bile ducts it was possible to obtain additional adequate drainage painlessly and without unfavorable reaction by incision or wedge-shaped resection of the exposed liver.

5. Hepatostomy of the exteriorized liver is suggested as a palliative operation to relieve the patient of intense jaundice and associated symptoms of ineradicable malignant disease when other palliative measures are ineffective.

6. Hepatostomy, with or without exteriorization, is suggested as a possible first stage procedure for congenital absence or occlusion of the extrahepatic biliary ducts when a single stage anastomosis to the gastrointestinal tract is unduly hazardous.

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THE SURGICAL APPROACH TO LESIONS OF THE UPPER SCIATIC NERVE AND THE POSTERIOR ASPECT OF THE HIP JOINT

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RECENT experiences with wounds of the sciatic nerve in the gluteal region have emphasized the usefulness of an approach to this region, developed by one of us (H. C. N.). This approach has been found to be of great value in cases of gunshot wound in which numerous pieces of metal are embedded in the area, since it gives a wide exposure facilitating the location and removal of these foreign bodies. Further, it exposes the upper portion of the sciatic nerve well into the sciatic notch, an advantage not obtained by any other approach. Of interest to orthopedic surgeons is the exposure of the posterior aspect of the hip joint afforded by this incision.

The gluteal region and the upper portion of the thigh are widely prepared. As the patient lies prone, the incision is made from just above the posterosuperior spine of the ilium downward and outward in a sweeping curve that passes over the greater trochanter, thence medially to the midline of the thigh and downward for a variable distance (Fig. 1). The skin and superficial fascia are incised along this line, thereby exposing the fascia glutealis which is cut from the trochanter upward and inward to the region of the posterosuperior spine where the gluteus maximus muscle takes its origin. The muscle itself is not incised. The incision is carried downward from the trochanter just lateral to the insertion of the gluteus maximus muscle into the gluteal portion of the fascia lata, to the region of the gluteal sulcus. At this point it may be extended still farther downward along the insertion of the muscle into the linea aspera and then medially through the insertion, or may be carried across the lower fibers of the muscle to the midline of the thigh. The former requires a longer incision, while the latter calls for section of the lower fibers of the muscle. Both have been found satisfactory. Starting at the trochanter, the gluteus maximus muscle with its fascia is separated by blunt dissection from the underlying structures and is turned back like the cover of a book, with nerve and blood supply intact, so that the sciatic nerve lies exposed from the pyriformis muscle just below the sciatic notch to the point at which the nerve disappears beneath the long head of the biceps femoris. The gluteus medius, pyriformis, gemelli, obturator internus, and quadratus femoris muscles and the upper portion of the long head of the biceps femoris are all within clear view (Fig. 2).

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If the incision is extended down the thigh, the entire sciatic nerve may be exposed from the notch to the popliteal space, the biceps femoris muscle being swung up or down to uncover the mid-portion of the nerve as it passes beneath the muscle. The entire incision is relatively dry, no structure of importance is sectioned, and on closure the parts fall together without tension.

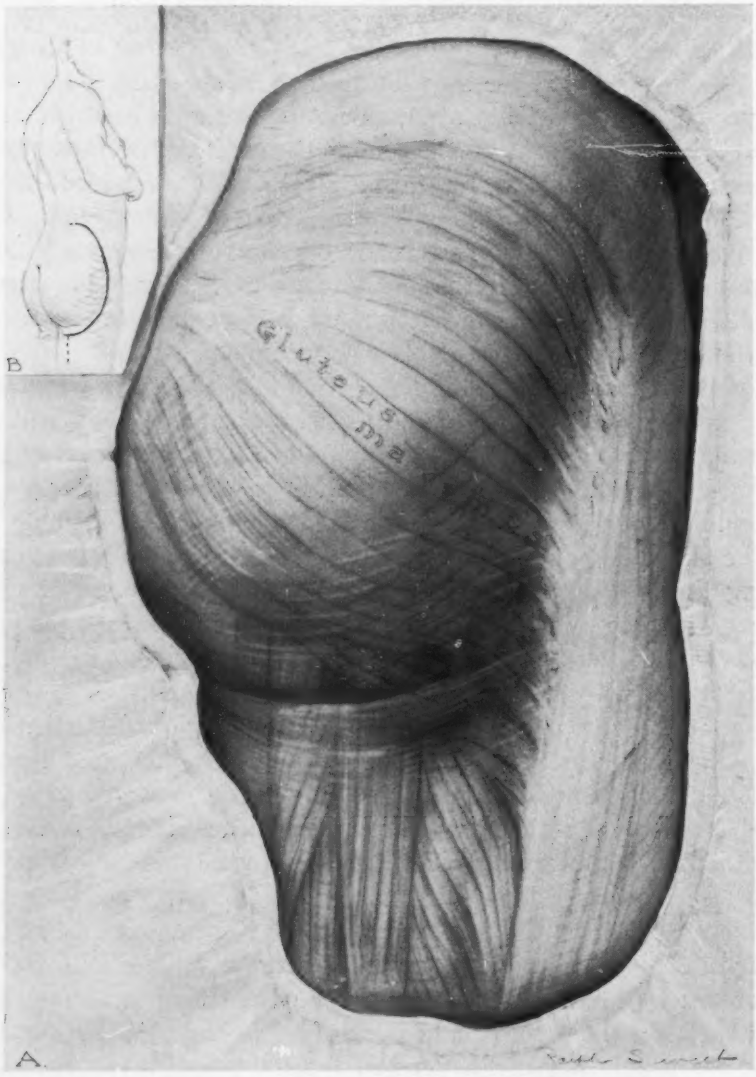

Fig. 1.—The back of the hip, showing *A* (as if transparent) the attachments of the gluteus and *B*, the skin incision.

A more limited exposure is begun in the same way but is extended only as far as the lower portion of the gluteus maximus muscle. This affords a fairly good exposure of the upper portion of the sciatic nerve and the posterior aspect of the hip joint.

ILLUSTRATIVE CASES

CASE 1.—R. M. G. was wounded, Dec. 7, 1941, by a piece of bomb case that entered the right gluteal region. His leg jumped straight out and became entirely numb.

He noticed no motor weakness. Sensation returned after one week and when he was first examined by us, Jan. 24, 1942, only a small spot over the posterior aspect of the thigh was anesthetic to pin prick. The Achilles and hamstring reflexes were absent. There was slight weakness of the flexor muscles of the thigh, leg, and foot, and these muscles were very tender. There was a great deal of spontaneous pain and cramping. X-ray examination showed a foreign body just below the lesser trochanter, 8.7 cm. beneath the skin at the gluteal sulcus. There was a small scar 3 cm. below and slightly lateral to this. At operation, performed under general anesthesia, the subgluteal region was exposed by the method described above. The sciatic nerve was somewhat swollen and harder than normal at a point about 5 cm. below the notch and just below the emergence of the nerve from beneath the pyriformis muscle. A hard object was palpated under this muscle and a fragment of a bomb case was removed without difficulty. The scar in the nerve was defined by injecting it with saline solution, causing ballooning of the normal nerve (Fig. 2) and outlining accurately the extent of the scar which occupied the outer one-third of the nerve. Neurolysis was performed. Crystalline sulfanilamide, 4 Gm., was dusted into

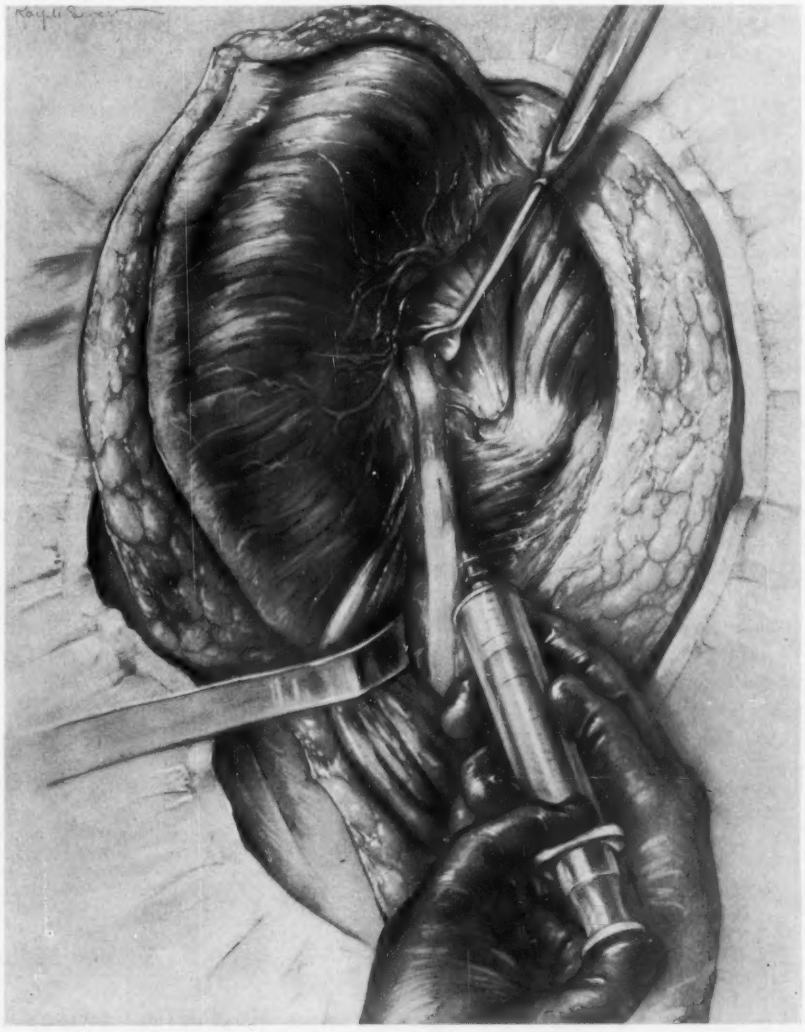

Fig. 2.—The complete exposure with the gluteus maximus turned back showing its nerve and blood supply, the sciatic nerve, the sciatic notch, etc. Note the injection of a scarred nerve with saline solution.

the wound. The cut portion of the gluteus maximus muscle was sutured by several mattress stitches of catgut and the deep fascia closed by interrupted silk sutures. The superficial fascia and skin were closed by interrupted silk sutures without drainage. The wound healed well, the patient being out of bed on the seventh day, and the sutures were removed on the tenth. The spontaneous pain was completely relieved and the soreness of the muscles was lessened considerably. Some cramping remained but has slowly improved.

On March 24, 1942, the Achilles and lateral hamstring reflexes were still absent but the medial hamstring reflex had returned. No motor weakness was demonstrable. The sensory loss remained unchanged. In short, slight but definite objective and considerable subjective improvement had occurred.

CASE 2.—B. J. H. was struck by machine-gun bullets, Dec. 11, 1941. The wound of entrance was in the upper right gluteal region and two fragments had lodged deep in the adductor longus muscle. Numerous metallic fragments were scattered along the line of the projectile which had fractured the acetabulum. The patient was first seen at the Mare Island Naval Hospital on Jan. 2, 1942, complaining of very severe pain which radiated down the back of the right leg to the foot. The Achilles reflex was absent. There was a little sensory loss in the foot over the distribution of the fifth lumbar and first sacral roots. Slight weakness was noted in the muscles of the leg, both anteriorly and posteriorly, and there was some uniform wasting of the leg. The gluteus maximus muscle was completely paralyzed and greatly atrophied. Because of the severe pain, requiring morphine, exploration was decided upon. On Feb. 4, 1942, the incision described above was carried as far as the lower fibers of the gluteus maximus muscle without cutting them. The muscle was reflected and the region of the sciatic nerve exposed. Three fragments of metal were found embedded in scar tissue on top of the nerve and there was a small abscess just medial to the nerve which itself seemed to be intact. The abscess, scar tissue, and metal fragments were removed by blunt dissection. The wound was thoroughly irrigated, crystalline sulfanilamide, 5 Gm., was dusted in, and closure was made with one layer of deep silkworm-gut sutures. Cultures from the abscess showed no growth and the wound healed by first intention, the sutures being removed on the tenth day. Following operation the severe pain in the leg and foot was completely relieved and the patient had no complaint referable to the sciatic nerve. At a subsequent operation an abscess in the adductor longus muscle was drained and more metal fragments were removed.

Examination, March 29, 1942, showed that the right Achilles reflex was still absent. The moderate degree of generalized weakness of the leg was unchanged and, as before, included muscles innervated by the femoral as well as the sciatic nerve. Sensation in the first sacral dermatome had returned but that of the fifth lumbar still showed some loss. There was no improvement in the atrophy of the gluteus maximus muscle. The patient had no spontaneous pain but complained when the soleus muscle was squeezed. There was little pain over the nerve and he walked fairly well without support.

SUMMARY AND CONCLUSIONS

A wide exposure of the gluteal and sciatic region is described and illustrative cases are presented. Its advantages are:

1. It is quickly and easily opened and closed.
2. The exposure of the region is perfect.
3. No important structures are sectioned.
4. The search for foreign bodies in this area is greatly facilitated and, in point of time, this alone more than compensates for the long incision.

POSTOPERATIVE ("ANESTHETIC") PARALYSIS OF THE BRACHIAL PLEXUS

A Review of the Literature and Report of Nine Cases

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(From the Division of Surgery, University of California Medical School)

PREVENTABLE injuries to the unconscious patient upon the operating table are, fortunately, infrequent though they occur more often than might be suspected; reports of such injuries are likely to be suppressed because of medicolegal complications, and many of the younger surgeons are entirely unaware of the possibility of such an occurrence. Some of those who do know of it have learned by the bitter experience of obtaining a perfect operative result only to have the patient disabled because of mishandling during his period of unconsciousness. In war surgery, when many operations will necessarily be done under great stress, it is imperative to have this complication ever in mind. Foresight on the part of the responsible surgeon may save weeks of disability for men in the armed forces.

Among such preventable injuries, that to the brachial plexus is all too common. Büdinger,[1] of Billroth's clinic, was the first to report such an injury occurring at the operating table, though other surgeons undoubtedly had been fully aware of this complication. Numerous articles were written during the latter part of the nineteenth and the early part of the twentieth century,[1-10] but these serious and wholly preventable injuries have received little consideration recently.[11-13] They are of such discredit to the surgeon, however, that they should be brought more prominently to the attention of the profession.

At first such injuries were attributed to anesthesia itself, but proof was soon forthcoming that they actually result from the patient's position on the operating table, which the surgeon frequently fails to supervise. Furthermore, he may be thinking more of his operative convenience than of a position of comfort for the patient.

The mechanism involved in injuries to the brachial plexus has been the subject of much debate. Büdinger explained such trauma upon the basis of pressure between the clavicle and the first rib; Krumm[2] believed that the nerves were compressed between the clavicle and the transverse processes of the fifth and sixth cervical vertebrae, and Braun[3] thought that the explanation lay in the compression over the head of the humerus while the arm was in external rotation and extension. Further studies seem not to have substantiated these ideas. It seems more logical to assume that injury to the brachial plexus received while the patient is anesthetized may have the same mechanism common to most injuries to the plexus, namely, tension. Gerdy is credited

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by French authors with originating the theory of traction, although others mentioned paralysis following a direct pull in the reduction of a dislocated shoulder.[14, 15] Horsley[4] emphasized the importance of a spread between the shoulder and the head in the production of these

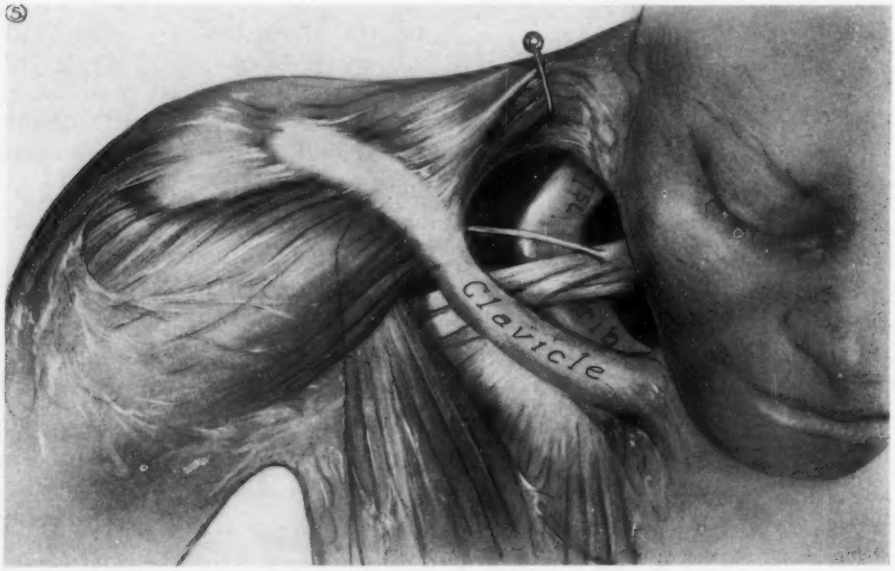

Fig. 1.—Normal anatomy of the brachial plexus in relation to the first rib, clavicle, and pectoralis minor muscle.

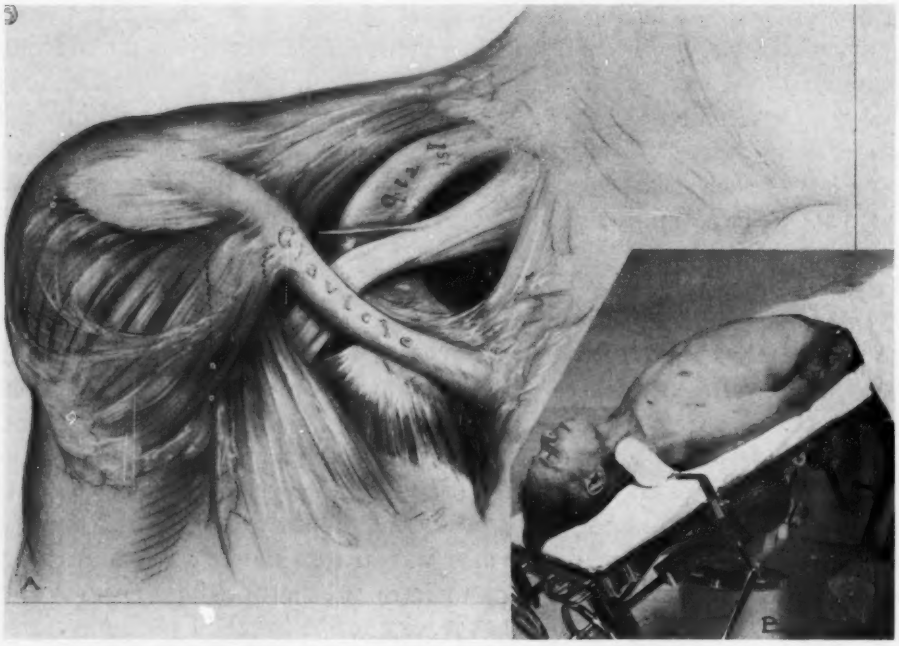

Fig. 2.—*A*, Anatomic drawing showing the arching of the plexus as it passes over the first rib when the arm is pulled downward in adduction. *B*, The patient is in the Trendelenburg position, suspended by the arms (the shoulder braces which should take the weight were not properly adjusted) with resultant increased tension as shown in *A*.

injuries and Stevens[16] agreed with the theory of tension, presenting mechanical evidence in its support.

A number of factors may be contributory. To appreciate all of these, the anatomic relationships of the plexus in relation to the first rib, the clavicle, and the pectoralis minor muscle must be borne in mind (Fig. 1). The injury is essentially one of stretch. Anatomically the nerves are fixed at the transverse processes by invaginations of the prevertebral fascia and in the arm by the axillary fascia. Any structure or structures, whether in a normal or an abnormal position, tending to increase beyond normal limits the distance between the points of fixation of the nerves, will cause injury. The structures involved are listed below.

1. The arch formed by the tendinous attachment of the pectoralis minor to the coracoid process of the scapula acts as a fulcrum in the axilla around which the neurovascular bundle passes. With movements of the shoulder, this arch changes so that the fulcrum is maintained in a neutral position preventing abnormal tension on the nerves. When the arm is pulled downward in adduction the first rib instead of the arch becomes the fulcrum (Fig. 2, *A*). When the arm is elevated, the scapula rotates and the entire shoulder girdle moves upward so that the fulcrum seeks a level which ordinarily does not interfere with the nerves as they pass into the arm. Should the shoulder be depressed while the arm is in abduction, however, the arch is low and the neurovascular bundle must pass around it to enter the arm (Fig. 3, *A*).

2. The clavicle also has a place in the consideration of these injuries. When the arm is by the side, the clavicle lies in an oblique lateral position. When the arm is drawn backward, the clavicle assumes a more anteroposterior position and depresses the plexus into the rectroclavicular space. If the arm is carried behind the back and drawn downward and across to the opposite side, the radial pulse will disappear. Compression of the subclavian vein by the first rib and the clavicle has been demonstrated by Sampson, Saunders, and Capp.[17] In extreme abduction and extension the clavicle actually compresses the plexus against the first rib (Fig. 4, *A*), though it is not this compression which causes the injury but rather the increased tension on the nerves distal to the area of compression. In Fig. 4, *A*, the nerves can be seen to be not only compressed in their proximal course but clearly on tension distally.

3. Lateral deviation and extension of the head have been known to produce injuries to the plexus, particularly when the shoulder is depressed. Horsley demonstrated this emphatically by dropping cadavers so that the impact was sustained with the head in abduction and the shoulder depressed. Frank rupture of the plexus resulted. Obviously, any abduction would tend to increase the distance between the arm and the transverse processes with resultant tension arising from other abnormal conditions.

4. With the arm in external rotation, abduction, and extension, the head of the humerus produces an axillary prominence around which the nerves must pass (Fig. 3, *A*). This can readily be seen at the time of the axillary dissection during a radical mastectomy. The injury is not produced by pressure on the nerves of the head of the humerus, but indirectly by increasing the distance between the points of fixation.

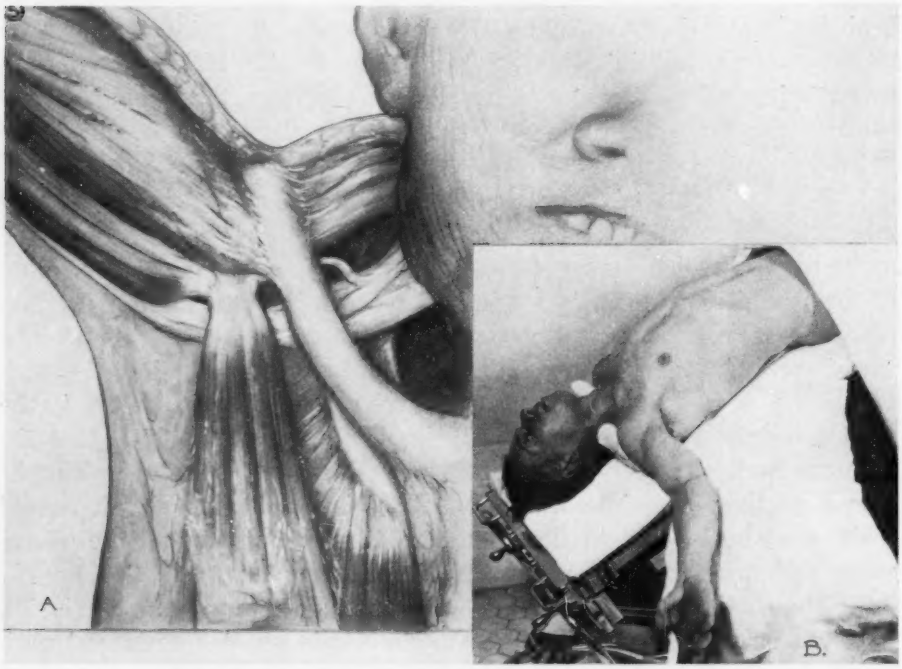

Fig. 3.—*A*, Anatomic drawing showing the position of the plexus when the arm is in external rotation, abduction, and extension; the prominence of the head of the humerus and the arch formed by the tendinous process of the pectoralis minor muscle are seen to put the plexus on increased tension. *B*, The patient's arm is in abduction in preparation for intravenous medication; the shoulder brace prevents the shoulder from shifting upward; consequently the plexus assumes the position shown in *A*.

5. Several of the foregoing factors are not involved when the arm is drawn downward forcefully. The first rib, however, becomes the fulcrum or prominence over which the nerves pass (Fig. 2, *A*). In those positions in which the clavicle is depressed into the retroclavicular space, the first rib also plays a part in the mechanism of injury by preventing the structures from falling back away from the clavicle, and consequently the plexus may be compressed or at least directed through an S-shaped course.

Injuries to the brachial plexus occurring on the operating table, actually, then, may result from any one of several factors which tend to increase the distance between points of fixation of the nerves, namely (1) the arch formed by the tendinous attachment of the pectoralis minor to the coracoid process, (2) depression of the clavicle into the retroclavicular space, (3) lateral deviation and extension of the head, (4) the prominence formed by the head of the humerus with the arm in external rotation, abduction, and extension, and (5) the first rib.

Congenital anomalies such as the presence of cervical ribs or an anomalous derivation of the plexus may make the nerves more vulnerable. For example, though the plexus is ordinarily derived from the fifth, sixth, seventh, and eighth cervical and first thoracic roots, it may originate at a higher or a lower level, thus, under certain circumstances, placing greater tension on the anomalous roots. Hypertrophy of the scalenus anticus muscle may play a part. These anomalies were not noted in the cases reviewed, nor were they encountered in our own patients.

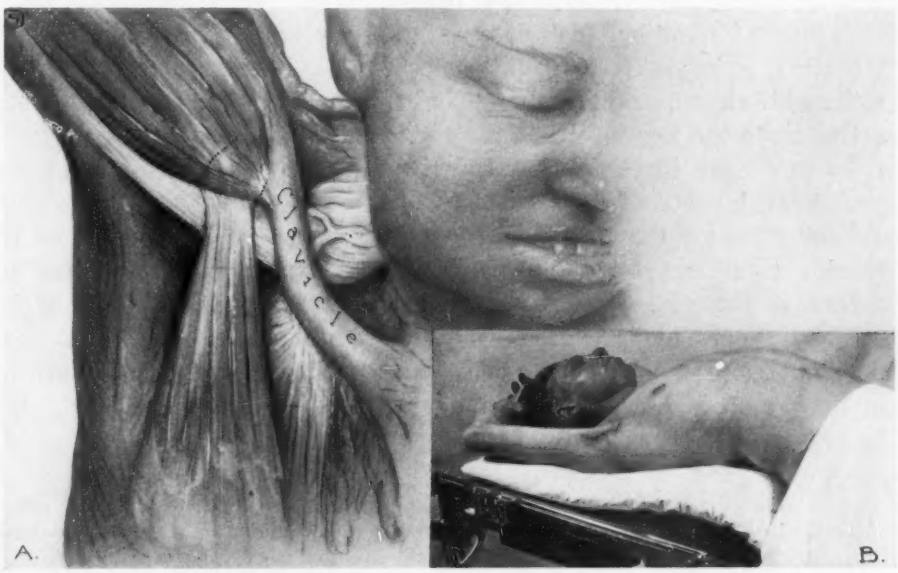

Fig. 4.—*A*, Anatomic drawing showing compression of the plexus by the clavicle against the first rib when the arm is in extreme abduction and extension; injury is caused primarily by tension on the nerves distal to the clavicle and the first rib. *B*, A patient in this position will show the anatomic features illustrated in *A*.

During anesthesia, musculotendinous protection is partially or entirely absent. Consequently, there is little resistance to exaggerated positions which result in increased tension upon the plexus as well as the subclavian artery and vein. These positions must be avoided and all movements of the patient must be attended by an adequate personnel.

Pathologic changes are seldom seen. Büdinger[1] made one post-mortem examination but was unable to detect either macroscopic or microscopic changes within the nerves. This has been the experience of surgeons who have examined the plexus at the time of operation following uncomplicated injuries to the plexus associated with traumatic paralysis. There have been, however, reports of ecchymosis, exudate, or scar of the fascial envelopes and fibrous septa in the nerve trunks noted at operation.[18-20] Actual rupture is extremely rare even in traumatic cases,[21-23] and no report was found of such an occurrence in so-called "anesthetic paralysis."

The diagnosis can be made readily if one is aware of the complication, though minor injuries with transient impairment of function may

frequently pass unnoticed. Paralysis, partial or complete, is noted immediately upon awakening. The patient may complain of anesthesia, hyperthesia, hyperesthesia, or paresthesia. In general, sensation seems less affected than motor power, or it may not be involved at all. Reflexes may or may not be present, depending on the severity of the injury. Tenderness in the supraclavicular space usually appears from five to ten days after operation, though local tenderness may be entirely absent. Ecchymosis has not been reported and was not present in this series of patients. Horner's syndrome is occasionally seen, indicating damage to the lower roots of the plexus.

Return of function, fortunately, is usually rapid and complete and sensation, if impaired, returns to normal quickly. An early return of reflexes, if they have been absent, indicates a return of function before active motor power is observed. Some muscular atrophy may result from prolonged inactivity but functional return was noted within one year in all but one of our patients.

Prevention of the injury is the prime consideration. There is no specific treatment for the paralysis. The arm should be placed in splints so that the muscles will be in a neutral position, and physiotherapy should be instituted early. The use of electrostimulation is debatable. Muscular atrophy may occur, depending upon the return of motor power. The patient's confidence must be gained and he must be assured of return of function.

CASE REPORTS

CASE 1.—D. S., 43 years of age, entered the hospital suffering from chronic cholecystitis with cholelithiasis. Her general health was excellent and no history suggestive of a vulnerable peripheral nervous system was elicited. A cholecystectomy was done under nitrous oxide and oxygen induction and ether anesthesia. The patient was in the supine position with the gall bladder lift in the lower thoracic region. Because the patient was thin and the arms resting on the table interfered with the position of the gallbladder lift, they were placed in abduction and hyperextension behind her head (Fig. 4, *B*). The procedure lasted two hours and forty minutes. The patient's recovery was uneventful except for paralysis of the brachial plexus, complete on the right and partial on the left. Preservation of function in the long and short flexor muscles of the fingers amounted to 25 per cent and that of the biceps, 10 per cent. Sensation was impaired bilaterally, but was more evident on the right than on the left. Bilateral Horner's syndrome was present. The reflexes were entirely absent except in those muscles partially preserved. There was no supraclavicular tenderness. X-ray examination of the cervical spine showed no abnormalities. Return of sensory function was first noted ten days after operation and was normal in two months. Return of motor function appeared first on the left during the third week after operation and was complete four months later. Return of such function was first noted on the right one month after operation and was complete ten months later except for the loss of extension of the thumb.

The position of choice for the arms is that of flexion over the chest. Damage to the brachial plexus, radial or ulnar nerves would then be impossible. In such a position, however, the elbows may be in proximity to the operative field and furthermore, should an infusion become necessary, some difficulty might be encountered in obtaining a

suitable vein. Consequently, at the University of California Hospital the arms are strapped to the side of the table, with the elbow well padded to prevent compression of the ulnar nerve.

CASE 2.—M. W., 31 years of age, entered the hospital for the correction of retroversion of the uterus and pelvic adhesions. With the use of nitrous oxide and ether anesthesia, dilatation, curettage, Webster suspension of the uterus, and left salpingo-oophorectomy were done. The operation lasted two hours and fifty-five minutes and the Trendelenburg position was used part of the time. The postoperative course was uneventful except for numbness of the left arm and pain and weakness of the left shoulder. The cords formed by the fifth and sixth cervical roots were the only nerves involved. The paralysis was not complete and hence the reflexes were present. Local examination of the shoulder suggested a tear of the capsule of the joint. X-ray examination of the shoulder and cervical spine showed no abnormalities. Recovery was complete in nine months.

With the wrists strapped to the sides of the table, a sudden change to the Trendelenburg position without proper adjustment of the shoulder braces had resulted in partial suspension of the body by the arm (Fig. 2, *B*). Since no muscular resistance was present, the tension was transmitted to the fascia and neurovascular structures with resulting injury to the upper roots. The mechanism was that of direct stretch over the first rib. This patient exemplifies the necessity of proper adjustment of the shoulder braces before the Trendelenburg position is assumed.

CASE 3.—H. C., 22 years of age, entered the hospital because of an abscess of the left upper lobe of the lung and chronic empyema on the left. With the use of nitrous oxide and oxygen anesthesia, a partial resection of the fifth and sixth ribs was done. The operation was completed in two hours and thirty minutes. The patient lay on his side with the opposite arm in marked abduction and internal rotation (Fig. 5). This position (the patient lying on his side) may cause lateral displacement of the cervical spine and the marked abduction of the arm causes stretching of the entire plexus. The lateral deviation of the head accounts for the preponderance of stress on the upper cords. Immediately upon awakening, the patient was found to have an incomplete paralysis of the brachial plexus with minimal sensory changes. The entire plexus was involved, but the paralysis of the upper roots, namely the fifth and sixth was complete. There was no supraclavicular tenderness or ecchymosis. Horner's syndrome was not present. No x-ray examinations were made, but there were no findings suggestive of cervical rib. Return of function was first noted on the seventeenth day after operation and was complete seven months later.

CASE 4.—G. E., 35 years of age, had infectious arthritis of the right hip, with ankylosis. An arthroplasty of the right hip was done under avertin in amylene hydrate, and nitrous oxide and oxygen anesthesia. The duration of the operation was three hours and fifty minutes. Her position was similar to that described in Case 3 (Fig. 4, *B*). Upon awakening, she noted a partial paralysis of the brachial plexus involving chiefly the upper two roots. Hyperesthesia was present over the distribution of the fifth and sixth roots. No abnormalities were noted in the x-ray examinations of the shoulder and cervical spine. Within six weeks, sensation was normal and motor power was returning rapidly; six months later no evidence of injury remained.

CASE 5.—C. S., 67 years of age, entered the hospital for repair of a rectosigmoid stricture. With the use of ether anesthesia a Heineke-Mikulicz operation requiring four hours' time was performed. During the procedure a venoclysis was given into

the right arm while the patient was in the Trendelenburg position. Immediately after operation she was unable to move her arm. Sensation was unchanged, although at times she complained of pain in the region of the shoulder. Horner's syndrome was present. No cervical ribs were found. Supraclavicular tenderness was present, beginning on the third day. Within twelve hours a return of muscular power was noted and in forty-eight hours function was observed in all muscle groups except those innervated by the fifth and sixth cervical segments. By the thirteenth day after operation, power was present in all muscle groups except the deltoid which showed no evidences of return of function for one month. Pain persisted in the shoulder and was present even eleven months later, at which time there was atrophy and weakness of the deltoid and biceps muscles, though return of function was almost complete.

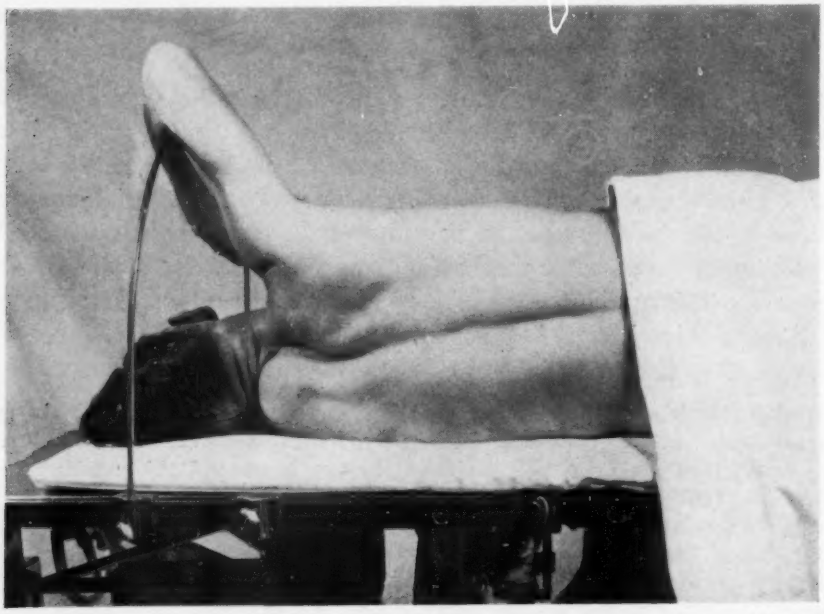

Fig. 5.—Position commonly employed for thoracic procedures, which resulted in injury.

CASE 6.—M. R., 26 years of age, was admitted for a hysterectomy which was done under ether anesthesia. A venoclysis was given into the left arm while the patient was in the Trendelenburg position. Upon awakening, she complained of numbness and inability to use the left arm. All muscles were paralyzed except for 25 per cent function of the flexors and extensors of the fingers. There was hypesthesia over the fifth, sixth, and seventh cervical roots and hyperesthesia of the eighth cervical and first thoracic segments. No Horner's syndrome was present and there was no evidence of cervical ribs. The muscular power returned rapidly so that by the eighth day after operation the biceps and coracobrachialis were the only muscles that had not regained full function. Sensation improved rapidly and was normal ten days after operation. Recovery was complete in two months.

CASE 7.—M. S., 51 years of age, was admitted to the hospital with chronic cholecystitis, cholelithiasis, and probable stones in the common duct. Under ether anesthesia, cholecystectomy and exploration of the common duct were done, the operation lasting two and one-half hours. An intravenous infusion was given into the left arm while the patient was in the Trendelenburg position. Immediately upon awakening she was unable to control her arm and stated that her hand was "still asleep." I first saw her on the third day after operation at which time no sensory findings were detectable. There was no paralysis but a weakness of all

muscles was present, the biceps and flexors of the fingers being most affected. On the twelfth day after operation muscular power had returned except in the biceps; this was normal when the patient was examined six weeks after operation.

CASE 8.—E. B., 53 years of age, was admitted to the hospital for the treatment of a rectal neoplasm. A combined abdominoperineal resection of the lesion was done. A blood transfusion was given into the right arm while the patient was in the Trendelenburg position. When the arm was being brought out in abduction, a clicking sound was heard in the region of the shoulder joint. Immediately after operation, the patient was unable to flex the forearm and the entire arm was numb. No paralysis of the hand and forearm could be made out. X-ray examinations of the shoulder and cervical spine showed no abnormalities. There was a gradual return of function, so that nine months after operation recovery was almost complete.

Cases 5, 6, 7, and 8 illustrate the most common mechanism of injury (Fig. 3, *B*). The shoulders are depressed and held in that position by the shoulder braces. With abduction of the arm, the entire plexus is put on stretch. The nerves arch over the first rib, pass under the clavicle, which is depressed into the retroclavicular space, as well as under the tendon of the pectoralis minor muscle, and finally around the head of the humerus. When the shoulder is held down by shoulder braces, the upper segments of the plexus will be more vulnerable, while if the shoulder is allowed to move upward, the lower segments will be more affected.

CASE 9.—An obese woman entered the hospital for a pelvic operation which was done with the patient in the Trendelenburg position. The shoulder braces, semicircular in pattern, were incompletely padded. Injury to the brachial plexus was the result of direct pressure of the brace which became interposed between the clavicle and the first rib.

Baldwin[24] reported three similar cases and proposed the use of the "Felter yoke." Shoulder braces must be well padded, adjustable in width as well as in height, and of sufficient depth in order to prevent the occurrence of such injuries.

SUMMARY

1. Nine cases of paralysis of the brachial plexus occurring in anesthetized patients while on the operating table are reported.

2. Unusual positions associated with complete relaxation result in abnormal tension on, and stretch of, the brachial plexus. The anatomic factors involved are shown to be lateral deviation and hyperextension of the head, the first rib, the clavicle, the arch formed by the coracoid process of the scapula and the tendon of the pectoralis minor muscle, and the axillary prominence of the head of the humerus.

3. Certain fundamental principles are emphasized.
   a. With the patient in the Trendelenburg position and the shoulder depressed, the arm should be left at the patient's side.
   b. When the arm is abducted, the head and neck must be held in neutral position or adducted.
   c. The arm should never be abducted beyond ninety degrees under any circumstances.

d. The arms must not be abducted and extended above the head when the patient is in the supine or the prone position.

e. Shoulder braces must be adjusted before the Trendelenburg position is assumed; they should be well padded and adjustable in height as well as in width.

f. Wide separation of the head and shoulders must be avoided.

g. Movement of an anesthetized patient must be attended by adequate personnel.

4. The possibility of this unfortunate complication must be kept in mind by every member of the operating room staff.

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PLATYBASIA

A Report of a Case Treated Surgically With Improvement

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PLATYBASIA (basilar impression), a rare disease entity even in the special field of neurology, has been slow both of general appreciation and of early recognition. Clinically, this condition is the result of the mechanical and neurological changes produced by a bulging upward of the bony structures about the foramen magnum, as if the bones of the skull in this region were softened and the skull were pushed down on an unyielding cervical spine. A diagnosis of multiple sclerosis, syringomyelia, or one of the various types of spastic paralysis, has often been made. Correct diagnosis in the early stages can probably never be made without the aid of roentgenograms. The present tendency, therefore, to x-ray all cases considered to be multiple sclerosis for a possible platybasia is a practice which should be encouraged.

History.—According to Ebenius,[4] the first description of platybasia was by Rokitansky in 1844, although DeVet[3] mentions a case described in the late eighteenth century. Boogard in 1865,[1] and Virchow in 1877[7] made detailed clinical studies of the condition, but to Schüller[6] goes the credit for the first clinical diagnosis by x-ray, in 1911. Platybasia was first brought to the attention of American neurologists by Chamberlain in 1939,[2] when he reported four cases at the Harvey Cushing Seventieth Birthday Celebration.

Etiology.—The etiology of platybasia, though still obscure, is probably an anomalous development of the basiocciput, and also, frequently, the upper cervical spine. The fact that most cases have an associated partial fusion of the spines of the upper cervical vertebrae gives credulence to this theory. Virchow[7] considered rickets, cretinism, hydrocephalus, idiopathic and puerperal osteomalacia, and senile atrophy as having only incidental etiologic significance. List[5] believes that not much proof has been offered to support the incrimination of rickets, Paget's disease, or osteomalacia. Trauma, due to repeatedly carrying heavy burdens on the head, is thought significant by Schüller,[6] who states that the condition is seen more often in countries where this is the practice. Weight-bearing or acute trauma has initiated symptoms or caused exacerbations of symptoms in a number of reported cases including our own.

Diagnosis.—The x-ray is the only certain means of diagnosis in all but far advanced cases. Chamberlain[2] has proposed the following empirical criterion for diagnosis: A line is drawn on a lateral x-ray film of the skull, from the posterior end of the hard palate to the dorsal

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Fig. 1A.

Fig. 1B.

margin of the foramen magnum (Fig. 1). If any of the cervical vertebral elements fall above this line, some degree of platybasia exists.

Chamberlain now considers the presence of an anomalous fusion, or failure of segmentation, at the level of the first cervical vertebra and the occipital segments of the spinal axis (the segments that go to make up the parts of the occipital bone which form the foramen magnum) necessary for the diagnosis of the type of platybasia which produces neurologic signs and symptoms.* The case presented in this paper does not show these anomalies and this viewpoint would, therefore, seem open to question.

A second method is determination of the basal angle, formed by the plane of the clivus and the sphenoidal plane, which runs through the root of the nose and the center of the sella turcica. The extreme limits of the normal range are 110° and 150° as given in the literature.

The neurologic picture of platybasia is partly produced by bony encroachment on the cerebellum within the posterior fossa, due to the upward bulging of the base of the skull. There is also probably some angulation or altered relations of the cerebellar peduncles, and this may be a factor in the production of cerebellar signs. Most of the medullary symptoms are the result of a sharp backward tilting of the axis and atlas, with pressure on the cord by the odontoid process, as the anterior weight-bearing portions of these vertebrae push farther into the cranial cavity than do the posteriorly placed laminae. The clivus is markedly elevated and presses on the pons. These altered relationships all contribute to impairment of posterior cranial and upper spinal nerves.

Because of the varied clinical picture which this condtion may present, it is helpful to divide the signs and symptoms into the following groups:

(1) Cerebellar: Nystagmus, atonia, clumsiness of the hands, staggering, and unsteady gait.

(2) Medullary and pontine: Pyramidal tract symptoms (increased deep reflexes, clonus, absent abdominal reflexes, abnormal plantar responses, and spasticity) and lateral spinothalamic tract impairment (dissociated sensory pain loss).

Tingling, pain, numbness, and weakness of the spastic type may all be produced acutely and often transiently by straining, sudden effort, or trauma.

(3) Cranial nerve: Palsies of the posterior group of nerves and those about the petrous ridges.

(4) Increased intracranial pressure: Headache, vomiting, choked discs, and blurred vision, from obstruction to cerebrospinal fluid circulation in the posterior fossa.

(5) Upper cervical peripheral nerves: Loss of sensibility in the corresponding dermatomes.

*Personal communication to Dr. R. Glen Spurling.

TABLE I

AUTHOR AND CASE NUMBER	PATIENT'S AGE	DURATION OF SYMPTOMS	SYNDROME	OPERATION	RESULTS
Ebenius[4] II	21	3 yr.	Increased intracranial pressure and cerebellar disturbance	September, 1932: "Suboccipital decompression through bilateral exposure of the cerebellum."	"Some improvement after operation."
III	59	6 yr.	Cranial nerve and cerebellar syndrome with shortened neck	November, 1933: "Suboccipital decompression."	"Only slight subjective improvement."
IV	46	2 yr.	Chiefly cerebellar	September (or October ?), 1933: Suboccipital decompression with resection of the arch of the atlas	Subjective improvement followed mild transient pharyngeal paresis
Chamberlain[2] I	20	5 yr.	Onset carrying canoe on head. Neck symptoms and medullary compression syndrome, the latter worse after being thrown on buttocks; remission twice after sedatives and lumbar puncture	June 30, 1937: Low occipital craniectomy with laminectomy of C 1, 2, and 3. Dura opened to inspect cord; negative findings	Clinical improvement measurable from the first postoperative day and has continued; entered medical school at age of 22
II	28	17 mo.	Medullary compression syndrome with cerebellum and cranial nerves about petrous ridges involved	Jan. 10, 1938: Low occipital craniotomy and laminectomy at C 1, 2, and 3; dura not opened	Improved markedly postoperatively; well until October, 1938 (9 mo.), when symptoms returned and patient died 15 days after readmission
List[5] I	21	22 mo.	Sudden onset pitching baseball; compression syndrome of medulla	(Laminectomy C 3 and 4 previously done with mistaken diagnosis tuberculosis of spine, in April, 1934.) March 28, 1935: Laminectomy C 1, 2, and 5. Foramen magnum decompressed on the left; bone graft applied occiput to C 5	Postoperative clot removed third day; patient died in few hours after temporary improvement. Postmortem examination showed typical bony changes with compression and softening of medulla

TABLE I—CONT'D

AUTHOR AND CASE NUMBER	PATIENT'S AGE	DURATION OF SYMPTOMS	SYNDROME	OPERATION	RESULTS
VII	24	2 yr.	Cerebello-medullary syndrome	Feb. 7. 1939: Funnel-shaped extension of occipital bone found over cervical dura; Arnold-Chiari malformation. Suboccipital decompression, extensive removal posterior rim of foramen magnum, and laminectomy of C 2 and 3 (C 1 assimilated into occiput); dura incised	Stormy postoperative course with clots removed twice; improved
Walsh, Camp, and Craig[8] I	46	22 mo.	Cerebello-medullary syndrome	November, 1940: Arch of atlas absent, C 2 and 3 fused, laminectomy C 2 and 3, posterior rim of foramen magnum removed, dura opened, herniated cerebellar tonsil found; adhesions present between meninges, cerebellum and pons freed	Marked improvement; six months later patient felt normal except slight weakness of left face and tongue
Stevens I	52	29 yr.	Cerebello-medullary syndrome with neck symptoms and upper cervical sensory loss	July 28, 1941: Suboccipital decompression, with laminectomy C 1, 2, and 3	Subjective improvement from first day; regression of neurologic signs continued 3½ mo. later. Patient back at work

(6) Non-neurologic symptoms: Neck pain, neck rigidity, torticollis, shortening of the neck, and feeling of weight and pressure in the neck.

From a consideration of these groups of symptoms, it will be seen that early cases, without increased intracranial pressure, and without sufficient bony change to alter the appearance of the neck, can closely simulate multiple sclerosis. Both conditions are usually manifested chiefly by cerebellar, cranial nerve, spastic and sensory signs. Moreover, the essence of the diagnosis of multiple sclerosis, i.e., remission of signs and symptoms, also occurs with platybasia. The mechanism of these remissions can only be surmised.

Therapy.—The resemblance to each other of early platybasia and multiple sclerosis is of major importance when one realizes that active therapy, always the prime consideration from the patient's point of view, is of doubtful value in multiple sclerosis and of definite, though possibly not permanent, value in platybasia. This therapy, undertaken in only eight previously reported cases, consists of removing the bone

from about the posterior rim of the foramen magnum and performing a laminectomy on the upper two or three cervical vertebrae. This bone removal, not in any way curative, relieves to a great extent the pressure on the cerebellum and posterior cranial nerves, and the angulation and constriction of the medulla at the foramen magnum. As DeVet[3] brings out, the bone so removed normally has no weight-bearing function, but with the altered relations in platybasia, the posterior arch of the atlas and posterior margin of the foramen magnum may be weight-bearing. If this is the case, acceleration of the progress of the disease after operation certainly must be considered a possibility.

Previously Reported Cases.—The reported cases of platybasia which have been operated upon therapeutically are summarized in Table I.

CASE REPORT

W. E. W., aged 52 years, salesman by occupation, was admitted to the neurosurgical service of the Norton Memorial Infirmary July 27, 1941 and discharged Aug. 11, 1941.

In 1912, at the age of 23 years, the patient, while playing football, forcefully struck the top of his head and experienced a momentary sharp shooting pain in the right ulnar region. It was not like that experienced when one strikes the ulnar nerve at the elbow.

In 1922, at the age of 33, for about a month, he experienced aching and tingling pain in the right hand, arm, shoulder, and upper thoracic spines. The pain in his arm and hand was just like that experienced in the football game in 1912. The ulnar region, beside being painful, was numb. This pain and numbness recurred approximately every two years until 1934, and was present at the time of hospitalization in 1941.

He has been impotent since about 1922, but has never had any sphincter disturbance.

From about 1926 until the present time, he has had double vision, especially on looking to the right. On July 1, 1929, his voice became very husky. For a year this recurred every morning after about thirty minutes of talking to customers, and would continue for the rest of the day. During this period he had a frequent "dry cough" associated with eating. The huskiness decreased in frequency until 1935 when it ceased, but the "dry cough" persisted. When first seen in 1936, he stated that he had had some dysphasia but did not recall this when questioned recently.

Since about 1930, the patient has noticed that hyperextension of his head was painful. His head has been slightly tilted to the right while at rest for the past fifteen or twenty years, he believes. His whole spine has ached to some degree for years. Since approximately 1931, his gait has been drunken in character and he tends to fall to the right. His left leg was "sleepy" for a while in 1930, and again markedly in 1933. Since 1932, he has had tinnitus and deafness in the right ear. He has never noticed any ataxia of his upper extremities.

The first neurologic examination on May 23, 1936, revealed the following positive findings:

(1) Some suboccipital tenderness on the right.

(2) Cranial nerves: Nasal side of each disc shows atrophy. III, IV, VI, well-sustained nystagmus on looking to the right; none on looking to the left. No rotary motions noted. Paresis of left external rectus and right superior oblique muscles. VIII, Twenty-five per cent loss of hearing in the right ear; fork is lateralized to the left.

(3) Cerebrum: Negative.

(4) Cerebellum: Definite swaying on standing with feet together, with a seeming tendency to fall to the right. Well-sustained nystagmus on looking to the right; none on looking to the left. Questionable dysarthria. Some dysmetria in the right arm with right adiadokokinesis.

(5) Sensory: Distinct loss of sense of position in both legs.

(6) Reflexes: Abdominals markedly diministed bilaterally. Scrotals sluggish. Deep reflexes equal and active. Plantars and confirmatories negative.

(7) Lumbar Puncture revealed initial pressure of 150 mm. of water; negative Queckenstedt; Wassermann and colloidal gold curve negative; cell count 2 per c.c.

A four months' trial on quinine-hydrochloride gave no symptomatic relief.

On Dec. 18, 1937, the patient exhibited spontaneous nystagmus on forward gaze, exaggerated on gaze to the right, and to a lesser degree on left and upward gaze, with some rotary component. He had constant diplopia with displacement chiefly vertical, but no obvious squint.

Caloric tests proved difficult to interpret (arrest of nystagmus when either ear was irrigated with 60 c.c. of cold water, but no dizziness was produced).

The patient walked on a broad base, and could walk tandem for only one or two steps before falling to one side, more often to the left. He was quite awkward at making turns while walking. No dysdiadokokinesis. Reflexes in the arms and legs were normal.

On March 9, 1939, no changes were noted.

X-ray examination of the skull made in July, 1941, showed the base of the skull to be definitely scaphoid in contour and the entire body of the first cervical vertebra and more than one-half of the second to lie above "Chamberlain's line." These changes were considered to be characteristic of platybasia. An axial view showed nothing unusual in the appearance of the foramen magnum.

The patient was admitted to the Norton Memorial Infirmary on July 22, 1941, and the neurologic examination showed the following positive findings:

(1) The patient held his head slightly to the right. Hyperextension of the neck was painful. There was no suboccipital tenderness.

(2) Cranial Nerves: Fields and fundi were negative. Nystagmus on right, left, and upward gaze. There was diplopia on gaze in all directions, although there was no obvious strabismus. The patient wore a patch over his right eye, feeling that this eye had more nystagmus than the left when used alone. The other cranial nerves were negative.

(3) Cerebellum: There was a suggestion of hypotonia in all the extremities. Rebound phenomenon was present in both arms. There was a mild cerebellar ataxia in the patient's gait, with a tendency to lurch to the right. Finger-to-nose and heel-knee-tibia tests were not ataxic. There was no adiadokokinesis.

(4) Motor: Negative.

(5) Sensory: There was hypesthesia over the second and third cervical dermatomes bilaterally except the "chin-strap" portion, where overlap probably renders loss imperceptible.

(6) Reflexes: Abdominal reflexes on the right were diminished. Cremasteric reflex on the right was not obtained. Other deep and superficial reflexes had a normal threshold and were equal bilaterally. There was no clonus, Hoffman response, or abnormal plantar responses.

Operation.—The operation was performed, July 28, 1941, under procaine infiltration anesthesia, with preliminary medication of nembutal, dilaudid, and hyoscine. The bone about the posterior rim of the foramen magnum was rongeured away and the laminae of the atlas and the axis were removed. No anomalies of these structures were noted. The dural sac was somewhat angulated as it disappeared beneath the lamina of the third cervical vertebra. Therefore, this lamina

also was removed. A small nick was made in the dura over the cisterna magna to determine whether or not it was obliterated. It was found to be full of fluid, and so the small hole was closed by placing a muscle stamp over it.

Postoperative Course.—On the third postoperative day the patient stated that his head, throat, and whole body had lost the feeling of "tension" which was present preoperatively. He could cough more easily and his "dry cough" feeling had gone. His body felt "livened up." He had practically lost the numbness in the right ulnar region.

One very interesting bit of history was elicited postoperatively. The patient stated that almost invariably upon arising in the morning he would have to "force his breathing" for about one-half hour. He was conscious of interference with the free automaticity of respiration. His sister, with whom he makes his home, described how she had noticed him taking frequent big deep breaths. This symptom disappeared entirely after the operation.

There was no change in the diplopia.

On the tenth postoperative day the patient stated that extension of his head was much freer and easier. In general, he felt optimistic and pleased with his condition. The neurologic examination however, was essentially unchanged when he was discharged on the fourteenth postoperative day. The following is a quotation from a letter received from the patient on Aug. 22, 1941, three and one-half weeks after operation: "I have been back home a week now and am still feeling fine and gradually picking up a little pep. I can't appreciate too much what you did for me and it looks now like it is not just a dream."

When seen on Nov. 13, 1941, fifteen weeks postoperatively, his status was improved. Diplopia was unchanged, but the nystagmus was less pronounced. He moved his head freely, his coordination was good, and his gait, though he still walked with a broad base, was improving. He has returned to work.

Comment.—In the case herein reported, trauma was the original precipitating factor, as has been noted by other observers. The extent of the role of trauma cannot be fully determined, but it probably acts in conjunction with a pre-existing condition to precipitate the syndrome or to cause an exacerbation of symptoms.

The remission of symptoms, which makes this disease so easily confused with multiple sclerosis, is well demonstrated here. The transient "huskiness" beginning after thirty minutes of talking every morning and lasting the rest of the day continued from 1929 to 1935. There was also some dysphagia during the same period. The huskiness and dysphagia may well have represented daily transient impairment of the vagus nerve after the patient had been in the erect position for a sufficient length of time each morning to allow the changed stresses of gravity to alter relations in the crowded and already strained posterior fossa.

The possibility of a long survival (twenty-nine years) with appreciable symptoms from platybasia is demonstrated. This is a much longer history than those obtained in the other reported treated cases, possibly because most patients with the clinical picture of multiple sclerosis do not continue under the observation of a physician once they have been reconciled to their diagnosis and the ineffectiveness of therapy. If this surmise is valid then every patient who has been dismissed with

a diagnosis of multiple sclerosis (or syringomyelia, or any other ill-defined degenerative spinal cord disease) should be contacted and investigated for the possibility of platybasia.

The advisability of incising the dura at operation is not agreed upon. Some authors believe that it should be opened in every case to search for anomalies of the nervous structures which might be amenable to surgical therapy. There was no reason to consider seriously the existence of an Arnold-Chiari malformation in this case, as the contour of the dural sac was not abnormal, and the cisterna magna was filled with fluid. The dura was therefore left closed and the nervous structures were thus disturbed as little as possible. The smooth convalescence and continued improvement seem to have justified this course of action in this instance.

SUMMARY

In platybasia the base of the skull about the foramen magnum appears to give way to the forces of gravity, and the unyielding cervical spine invaginates up into the posterior fossa. Pathology is manifested by interference with cerebellar, medullary, cranial nerve, and upper cervical nerve function. Increased intracranial pressure and various symptoms and signs referable to posture and movement of the neck are often present. The etiology, though still unsettled, is probably an anomalous development of the bony structures in the region affected. Platybasia, in its early stages, frequently produces a picture almost identical clinically to multiple sclerosis, even to the occurrence of remissions. X-ray pictures of the skull are necessary for diagnosis of all but far-advanced cases. Surgical therapy has been previously tried in eight reported cases. A ninth case with postoperative improvement is here described in detail.

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PRESERVATION OF THE TRANSVERSALIS MUSCLE IN GAS GANGRENE OF THE TRUNK

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THE importance of infection of muscular tissue in fatal gas gangrene was emphasized in World War I.[1] Qvist[2] differentiates the anaerobic cellulitis of nonmuscular tissues from the true gas gangrene with clinical toxemia produced by clostridial infection of muscular tissue. Multiple incisions are effective in the control of anaerobic cellulitis but complete excision of the infected muscle or muscle group is necessary for the control of true gas gangrene. A recent review of gas gangrene of the abdominal wall[3] fails to distinguish between anaerobic cellulitis and gas gangrene with muscular infection. It is believed that such a distinction is essential to any plan of treatment and that conservative measures are to be reserved for the management of anaerobic cellulitis.

True gas gangrene of the abdominal wall or trunk constitutes a surgical problem in that excision of the external and internal oblique and transversalis muscles destroys the integrity of the abdominal wall. In the following instance of gas infection of these lateral muscles the truly muscular external and internal oblique muscles were completely removed, but the infected transversalis muscle was left in situ because it was more fibrous than muscular and provided adequate support for the abdominal contents.

CASE REPORT

M. G. H. (Hospital No. 262448), male, aged 31 years, was seen on the evening of Aug. 8, 1940. The patient had suffered a stab wound of the abdomen twenty hours previously. Pain in the abdominal wound developed twelve hours after injury and crepitus was first noted eighteen hours after injury.

Upon examination the patient was moaning with pain, covered with perspiration, and in mild shock with cold, clammy extremities. The blood pressure was 88/40 with a thready pulse of 150. The temperature was 102° F. by rectum. Crepitus was demonstrable from the groin to the nipple, from the spine to the midline of the abdomen, and the scrotum was distended with gas and discolored by a hemorrhagic extravasation. There was a lemon yellow icteric tint to the skin and sclerae. The wound was a transverse laceration of the left upper abdomen, about ten inches long. From the partly separated wound edges there was protruding a large, dark blood clot possessed of a slightly putrid odor.

The patient was removed by ambulance to the Massachusetts General Hospital. Upon entry he was taken directly to an operating room. An intravenous infusion of saline solution was started and the patient received intravenously 6 Gm. of sodium sulfapyridine, 3 therapeutic vials of polyvalent gas gangrene antitoxin,*

*Lederle Laboratories, Inc.

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and 3,000 units of tetanus antitoxin. Blood transfusions were started. Within an hour the patient's general condition improved somewhat as evidenced by a rise in blood pressure to 100/60 and a fall in pulse rate to 120.

Under ether anesthesia the abdominal wound was reopened and explored. The tangential stab wound had perforated the abdominal cavity and lacerated the splenic flexure of the transverse colon. A profuse hemorrhagic exudate escaped from the peritoneal cavity. The splenic flexure of the transverse colon was mobilized and the bowel exteriorized in the wound and covered over with gauze. A longitudinal incision was made from the groin to the nipple through the middle of the original laceration. The skin and subcutaneous flaps of this cruciate exposure were reflected back. The muscular bellies of the external and internal

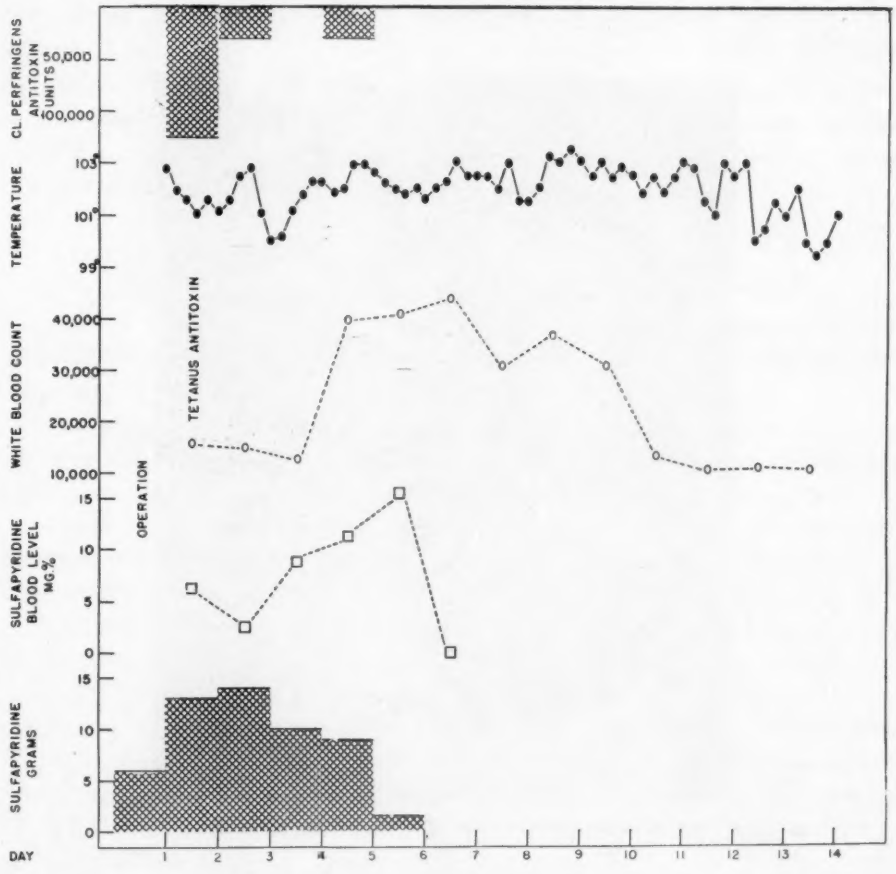

Fig. 1.—Summary of therapy and clinical course.

oblique muscles were crepitant and discolored. These muscles were completely excised from the lumbar aponeurosis to the rectus sheath, and from the groin to the level of the fifth rib. The inferior half of the pectoralis major had to be sacrificed in order to completely remove the underlying attachments of the oblique muscles. The crepitant transversalis muscle was in reality a fibromuscular sheet with very little muscle tissue and was therefore left in place. No attempt was made to expose all areas with obvious crepitus and the scrotum was not opened. This wound was dressed with zinc peroxide and the skin flaps allowed to fall in place. After a complete scrub and change of instruments, the upper right abdomen was entered through a transverse incision. A loop of transverse colon was

drawn up and severed with the actual cautery between clamps to establish a transverse colostomy and to defunction the left colon. At the conclusion of this procedure the patient's pulse was 110 and the blood pressure was 130/80. He was returned to the ward, transfused again, and given oxygen by the Boothby mask.

Postoperatively he received blood, antitoxin, and sulfapyridine as indicated in Fig. 1. The fever gradually subsided over a period of two weeks but was not entirely normal until the wound was completely epithelialized with the aid of skin grafts two months after entry. The transverse colostomy was closed on Oct. 18, 1940, and the patient was discharged shortly thereafter.

When seen one year after discharge the abdomen appeared as in Fig. 2. There was a hernia in the area of the exteriorized loop of splenic flexure of the colon. An abdominal corset was worn to protect the area of skin grafting as much as for the support it afforded. He was back at work as a prison guard and in good general health.

Fig. 2.—Abdominal scar one year after operation.

BACTERIOLOGIC STUDIES

Cultures of the wound and of the peritoneal pus were both positive for the following organisms: (1) *Clostridium perfringens,* (2) *Escherichia coli,* (3) alpha hemolytic streptococcus, (4) two strains of nonpathogenic aerobic Gram-positive sporeforming bacilli (subtilis group).

Special studies upon the *Cl. perfringens* included the following:

Toxigenicity.—(a) An overnight culture, 0.2 c.c., in cooked meat medium, killed intramuscularly injected guinea pigs in less than eighteen hours. At autopsy the heart's blood was positive for *Cl. perfringens.* (b) Passive immunization with specific perfringens antitoxin protected

guinea pigs against intramuscular infection with the strain. (e) Growth in human serum (Nagler[4]) and in egg yolk (MacFarlane[5]) produced opalescence and separation of the lipid element. This reaction was inhibited by specific antitoxin.

Cultural Characteristics.—(a) Morphology: nonmotile, Gram-positive bacillus with no visualized spores; (b) iron milk: stormy fermentation with no blackening; (c) lead acetate and Wilson-Blair plate: blackening; (d) nitrite: positive; (e) indole: negative; (f) iron gelatin: blackened and liquefied; (g) production of acrolein aldehyd from glycerin: positive; (h) violet: negative; (i) sugars fermented: sucrose, lactose, maltose, and dextrose; (j) sugars not fermented: mannite and salicin.

Studies Upon the Patient's Serum (Nagler Reaction).—At no time was it possible to demonstrate a sufficient excess of antitoxin in the patient's serum to inhibit the opalescent change as a consequence of growth of the *Cl. perfringens* in the serum.

COMMENT

A patient was successfully treated for gas bacillus infection of the abdominal wall and peritoneal cavity and true clinical toxemia following a stab wound of the colon. The etiologic organism possessed all the cultural attributes of the *Cl. perfringens* and was toxigenic.

Treatment consisted of local excision of devitalized tissue, defunctioning colostomy, zinc peroxide locally to the wound, sulfapyridine systemically, and antitoxin parenterally.

It is believed that the decision to remove the external and internal oblique muscles and to leave the transversalis muscle contributed to the successful outcome. The transversalis muscle is in reality a thin and fibromuscular structure in many individuals. Since true clinical toxemia is so often dependent upon infection of the muscle with gas bacilli[2] it would not seem necessary to excise a predominantly fibrous structure. The thinness of the tranversalis muscle increases the possibility of successful local treatment when the entire structure is exposed. Hence, it seems reasonable to recommend leaving the transversalis muscle to support the abdominal contents when faced with the problem of gas gangrene of the trunk.

The established gas bacillus peritonitis was promptly controlled by the exteriorization of the lacerated colon and proximal defunctioning colostomy. This is in accord with the established principle that fatal peritonitis from intestinal bacteria is associated with a continued fecal contamination from a faulty suture line or intestinal wound.

The administration of 140,000 units of perfringens antitoxin intravenously did not establish a sufficient circulating excess of antitoxin to inhibit the Nagler reaction. The serotherapy of gas infections is seriously handicapped by lack of data on the required dosage. The Nagler reaction offers a method whereby such dosage may be regulated.

Sulfapyridine was chosen because it was the available sulfonamide of choice in 1940. The zinc peroxide was locally effective against the *Cl. perfringens* but did not prevent troublesome secondary wound infection with *Esch. coli* and *Pseudomonas aeruginosa* (pyocyaneus).

CONCLUSIONS

1. In excising infected muscles for gas gangrene of the trunk it was practical to leave the more fibrous transversalis muscle as a support for the abdominal contents.

2. Perfringens antitoxin, 140,000 units, failed to establish a demonstrable excess of antitoxin in the serum.

3. Zinc peroxide was locally effective against the *Cl. perfringens* but did not prevent secondary wound infection with *Esch. coli* and pyocyaneus.

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EXTENSIVE, MUTILATING FACIAL DEFECT; COSMETIC CORRECTION WITH LATEX MASK

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ONE of the contraindications for plastic surgery as a method to repair facial defects is the presence of coexistent disease. Constitutional diseases like lupus, leprosy, and syphilis, by their devastating and frequently bizarre destruction, often make plastic surgery, as a method of reconstructing missing parts of the body, unwise. The debility which accompanies these diseases, as well as the fact that recurrences may often be expected, makes it difficult to decide upon surgical reconstructive operations for such conditions.

Yet many patients with facial defects caused by consumptive diseases are so disfigured as to create a distinct problem to cover their defects in such a way as to make them socially and esthetically acceptable. Heiser[1] mentions the problem of covering the horrible facial defects in individuals who have leprosy and in whom the disease has been arrested. Many of these patients, he states, remain in the leper colonies even though offered their freedom because they are esthetically unacceptable in their normal social environment.

A case in which extensive destruction of the face has occurred is here presented to demonstrate that a large latex compound prosthesis can be constructed and adapted to conceal unsightly, even open, lesions. It also indicates that a prosthesis of latex may be designed to cover moving parts, with comfort and esthetic satisfaction to the patient.

History.—S. A., aged 29 years, was referred by the department of dermatology, Northwestern University Medical School. His blood Wassermann and Kahn were 4+ and he had been treated for several years with antisyphilitic therapy. Destruction of the face was extensive, obliterating the features of the entire face below the eyes. Although several areas on what remained of the face bore weeping ulcers, the patient's condition was more or less quiescent, and although he had been taking his treatments faithfully, he found the treatments did not improve his appearance and he was desperate for some means to disguise his repulsive face.

The patient presented himself wearing a bandage completely covering his face and head with only the ears and eyes exposed. As he unwound his bandage he warned me, saying, "Doctor, my face looks really bad." As illustrated, he exposed a face hideously disfigured. The nose had completely sunk into the nasal cavity, obstructing the airway, the cheeks were gone and were represented only by scar tissue bound down upon the malar bones. The upper and lower lips had disappeared leaving the alveolar ridges and anterior teeth exposed. The skin of the chin and lower jaw was replaced by scar fixed to the mandible. The motion of the mandible was almost completely limited by the scar tissue and by ankylosis of the jaw. The lower eyelids showed mild symptomless ectropion. Saliva drooled over the mandible and could only be controlled with gauze sponges fixed inside the bandages. What remained of his skin was too fragile to permit shaving.

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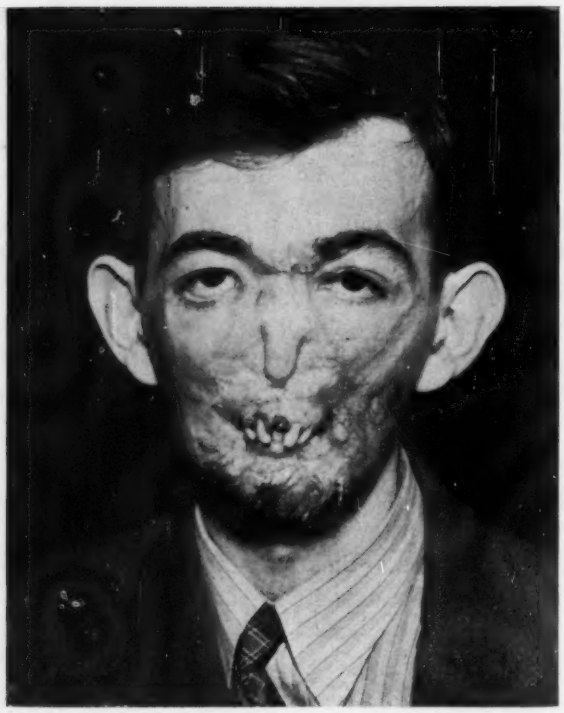

Fig. 1.—Inoperable mutilating deformity caused by malignant syphilis.

Fig. 2.—Profile before prosthesis.

Mentally, the man showed no signs of deterioration, was well oriented as to his position, and very bitter about his plight. He lived in the hospital, never permitted himself to be seen without his bandage, and told me that he had not looked in a mirror for over three years. As a form of self-imposed discipline, he had destroyed all his photographs. Although there is no precedent for a prosthesis so large, we decided to make one.

Technique.—With antisyphilitic precautions, vaseline was applied over the entire face. A negative impression of the entire face was made with molding plaster. The negative impression was removed, soaked in lysol solution for several hours, and while wet, coated thinly with mineral oil. A positive impression of the face was made by pouring a mix of dental stone into the negative impression. The negative was removed, leaving a stone likeness of the face. In order that the prosthesis

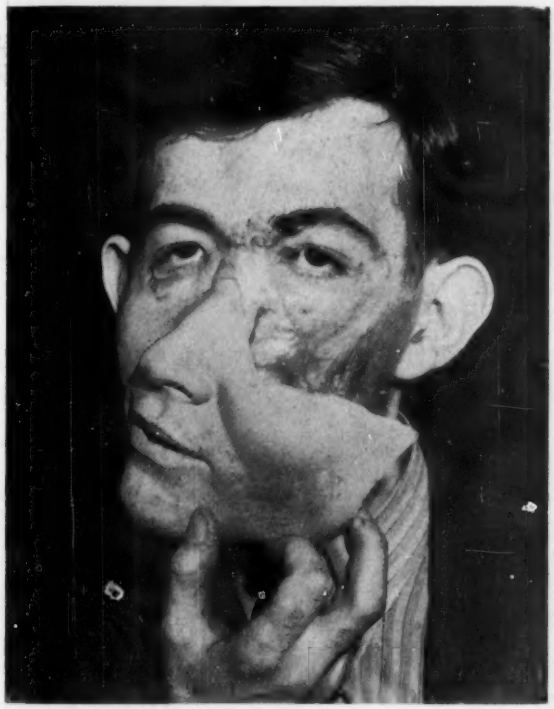

Fig. 3.—Prosthesis being applied with gum mastic mucilage.

should be shouldered upon only sounder tissue, the portions of the face which were ulcerated were covered upon the positive cast with additional layers of plaster. This was also done about the lips and teeth to allow for airway, and below the chin to allow for shrinkage of the rubber compound during molding. This space was also necessary to provide a place within the prosthesis for cotton sponges to collect saliva.

Upon the positive cast a new face was sculptured in clay. The features were so constructed as to leave the mouth slightly opened to allow for ventilation. Our aim was to construct a face with regular features but commonplace enough as not to draw attention to the wearer

Fig. 4.—Patient with latex rubber prosthesis. Glasses are worn for esthetic effect; spectacle frame not used for support of mask.

Fig. 5.—Profile with prosthesis; cotton sponges in chin portion collect the saliva.

of the rubber restoration. The lips were modeled with a hint of a smile. The pores of the skin were reproduced by pouring a small mix of fresh plaster over the skin of a normal face. When dry this piece of plaster was used as a tamp to impress the pores and delicate skin tracery into the clay.

The ensemble of the positive cast bearing the clay face was then covered with a fresh batch of dental stone to form two halves of a two-piece mold containing the clay restoration between them. When hardened the two halves of the mold were separated and the clay washed out. The parts were thoroughly dried, reassembled, and were then ready for the molding of the rubber. In order to simulate a shaven skin, electric shaver clippings were thinly spread upon the inner surface of the outer half of the mold. When the mold was poured with precolored latex compound the fine beard shavings thus became imbedded in the visible surface of the prosthesis. This ruse proved quite realistic.

The inside of the superior and posterior edges of the restoration are coated with a gum mastic mucilage when the patient is about to put on his mask. As shown in the photographs, the spectacle frames bearing slightly tinted lenses obscure the feather edge of the prosthesis.

The transformation is astonishing. The patient, after several years of idleness and despair, has now been given a light part-time occupation and is quite happy, even proud, of his prosthesis. The artificial face has made this patient's life endurable.

This work was done under the direction of Dr. Francis Lederer, who first developed flexible translucent prostheses in this country.

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Editorial

The Questionnaire Method for Standardization

IN RECENT years there has arisen the pernicious habit of sending out questionnaires in order to tabulate many aspects of medical practice. When these are circulated by some individual who wishes to acquire information for a scientific article, a minor evil arises. Such questionnaires are a bother to the colleagues who have to fill them out. As a result, they are always loosely answered, since those who reply to the questionnaire do not have the time to conduct a serious investigation of the problem. Naturally, their time is spent doing their own work rather than doing that of others.

But when the questionnaire involves the standardization of surgical methods we have a much more serious problem. Any scheme of standardization obtained by means of the questionnaire method means that the standard thus obtained will be mediocre for this method compiles the average, not the best, methods. This is beginning to be apparent in more ways than one. If, for example, the sponsors of a recent questionnaire on the standardization of sterilizing technique summarize the usual practice, they will put before the profession the average, not the best, method. Leaders in the profession should not be desirous of standardizing methods at an average level but should push the standards ever higher, up to the highest now known, perhaps even higher, and then try to elevate the institutions up to that high level. This is the only method by which progress can be made.

It appears that standardization through the questionnaire method is but a part of the general threat of the regimentation of people in our country. There seems to be a peculiar lack of personal initiative. There seems to be a desire to conform to the ordinary as opposed to the extraordinary. There seems to be satisfaction with mediocrity as well as the desire for all to walk in the same line and in the same fashion. It may be that the regimentation of our people, as evidenced by what the Government has been trying to do for years, is now exerting its hold on the profession of medicine and we are soon to see standards reduced rather than elevated. It is hoped that the profession will be awake to such destructive ideas and that, at least as regards surgery, we will try to individualize our work at the highest possible peak. If we adopt this attitude, the care of the thousands of young men soon to be our responsibility will be perceptibly bettered.

—Elliott C. Cutler, M.D.
Boston, Mass.

Announcements

American College of Surgeons Cancels Clinical Congress

The annual Clinical Congress of the American College of Surgeons which was scheduled to be held in Cleveland, Nov. 17-20, 1942, was cancelled by the Board of Regents of the College at a meeting held in Chicago, Wednesday morning, October 14. Motivated primarily by patriotism, the Regents were influenced by the present conditions surrounding the general war program which have led to a greater burden on the members of the surgical profession in their local communities as a result of the large proportion of the profession which is serving with the armed forces. The Regents by this action took cognizance of the desire of the profession to do nothing which would interfere with the successful prosecution of the war program such as would be caused by temporary absence of its members from civilian duties during the period of the Congress, embarrassment of the transportation system, and interference with the work of the local profession in Cleveland in preparations and presentations incident to such a meeting.

The Activity of the Medical and Surgical Relief Committee of America in the Collection of Medicine and Instruments for Military Purposes

At the recent meeting of the Medical Society of the District of Columbia, held Sept. 29-Oct. 1, 1942, a completely equipped emergency medical field set was donated to Vice Admiral R. R. Waesche of the U. S. Coast Guard by the Medical and Surgical Relief Committee of America, a relief organization with headquarters at 420 Lexington Avenue, New York, N. Y. Ten similar sets have been turned over to the Coast Guard, bringing the total number furnished by the Committee to first-aid posts, emergency medical centers, needy hospitals, and other recognized relief agencies up to 233.

Each of the sets consists of two portable cases completely equipped with instruments, medicines, antiseptics, and a lantern with a set of dry cells to provide power for lights in the event of blackouts or power difficulties. The sets were designed by physicians after a series of experiments during bombing attacks on London.

The campaign to furnish emergency medical field sets is only one phase of the work in which the Committee has been actively engaged since its inception in August, 1940. Organized by Mrs. Millicent Huttleston Rogers and a few New York City physicians to send surplus medicines and surgical instruments to physicians in Great Britain, it has since grown to a nationwide committee consisting of approximately 500 physicians and surgeons assisted by an equal number of professional and non-professional volunteers.

With the spread of war, the organization's scope has broadened to take care of requests from Greece, China, Russia, the Royal Norwegian Forces in Iceland, and the Free French Forces in Northern Africa and Miquelon. Since Pearl Harbor, primary consideration has been given to America's needs.

To date, medical supplies and surgical instruments valued at $475,690.05 have been sent out by the Committee. The supplies are collected from physicians, hospitals, pharmaceutic houses, and drug stores, then sent to the Committee's New York headquarters. Medicines are sorted and rebottled under the supervision of trained nurses. Instruments are polished, and if necessary, reconditioned. They are then redistributed to organizations where the need for them exists.

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

THE PROBLEM OF THE BLEEDING PEPTIC ULCER

A REVIEW OF 284 PATIENTS ADMITTED TO HARPER HOSPITAL DURING THE YEARS 1931 TO 1941

M. JORDAN THORSTAD, M.D., DETROIT, MICH.
(From the Harper Hospital)

THE most common complication of peptic ulcers is hemorrhage. Acute massive hemorrhage is manifested by vomiting of blood (hematemesis) or the passage of tarry and bloody stools (melena) together with signs of shock, such as, paleness, weakness, air hunger, dyspnea, collapse, weak and thready pulse, and low blood pressure. The chronic type of hemorrhage is characterized by the presence of tarry stools for many days, resulting in a progressive anemia and subjective symptoms of weakness, vertigo, and malaise.

INCIDENCE

The incidence of hemorrhage as a complication of peptic ulcer is variously reported in the literature as from 18 to 20 per cent.[39, 43-45, 84, 102, 104] This disease is four times as common in the male as in the female.[18, 20, 43] The incidence of gross hemorrhage reaches its peak during the fifth decade and approximately 70 per cent of the cases occur in patients past the age of 40.[34, 44] Vital statistics reveal that 70 to 90 per cent of all deaths from this disease occur in patients over 45 years of age.[6, 14, 15, 18, 34] The incidence and mortality rate increase with age and the presence of arteriosclerosis and hypertension. Many men emphasize that approximately 50 per cent of all patients over 45 years of age who bled from ulcers have had the acute massive type of hemorrhage.[6, 19, 20] Alsted[7] has found in Denmark that the incidence of hemorrhage from peptic ulcers has increased but that it is less severe.

ETIOLOGY

Hemorrhage from a peptic ulcer is initiated by many different factors. From England, Melton[81] has reported a marked increase in the incidence of bleeding peptic ulcers after the outbreak of the war. He found that the abnormal increase in mental and physical strain was the most common etiologic factor. Abuse of the use of alcohol and tobacco,[105] as well as dietary indiscretions, often are the inciting causes. Focal infections,[92] such as dental caries and abscessed teeth, and infections of the upper respiratory tract[34, 88] may cause bleeding from peptic ulcers.

External trauma about the abdomen and unusual physical exertion, particularly heavy lifting,[92] have been associated with this disease. Vitamin deficiencies, especially vitamin C, developing from the limited diet of the patient suffering from an active peptic ulcer are thought to be an etiologic factor.[66, 102] Snell[102] also mentions a possible vitamin K deficiency. However, nervous and emotional strains seem to play the major role in provoking hemorrhage from gastric and duodenal ulcers.[7, 34, 43, 66, 81, 102]

SYMPTOM COMPLEX

The onset and train of symptoms in acute massive hemorrhage are quite characteristic. The patient is often at work when he experiences a sudden sensation of nausea together with a feeling of weakness, unsteadiness, and vertigo, following which he may vomit a variable amount of bright red blood or coffee-ground material. Frequently he collapses and shock is manifested by a cold and clammy skin, paleness, dyspnea, air hunger, and thready rapid pulse. The blood pressure is low and the temperature is often subnormal. Bowel movements are either bloody or tarry in nature. Epigastric distress may or may not be present; if present, vomiting or the taking of an antacid drug will give relief.

PATHOLOGY

Hemorrhage from the upper gastrointestinal tract may occur in the presence of diffuse gastritis, carcinoma of the stomach, rupture of esophageal varices, purpuras and blood dyscrasias, polyposis of the stomach, and most commonly from gastric or duodenal peptic ulcers. Rivers and Wilbur[92] of the Mayo Clinic found that peptic ulcers were responsible for more than 85 per cent of the cases of hematemesis due to intrinsic gastroduodenal lesions. At operation, and even at autopsy, it may be difficult to discover the source of the hemorrhage if bleeding has stopped temporarily.

Duodenal ulcers are more frequently the source of the hemorrhage than are gastric ulcers.[92] Hemorrhage from a posterior duodenal ulcer is the most likely to prove fatal. The most severe and persistent type of bleeding results when the pancreaticoduodenal arteries in the posterior wall of the duodenum and the left gastric artery and the gastroepiploic artery in the posterior wall of the stomach are involved. Wilmer,[109] who carefully studied the blood supply of the first part of the duodenum, found that there are two pancreaticoduodenal arcades. Uniting these arcades are large anastomosing vessels running for a long distance on the posteriomedial wall of the duodenum. These vessels, in turn, join smaller anastomosing vessels which constitute the very vascular network of arteries which Wilmer calls the *gastroduodenal plexus.* Erosion of one of these larger posterior vessels of this plexus probably causes the acute massive hemorrhage, as compared to the slow chronic hemorrhage due to erosion of the submucosal vessels.

Acute massive hemorrhage from an ulcer usually occurs following an injury to the wall of a small blood vessel. If the vessel is severed transversely, the bleeding end ordinarily retracts and hemorrhage may be only transient. If a section of the wall sloughs out, retraction is difficult and hemorrhage is prolonged. Arteriosclerotic changes in the vessel wall also interfere with retraction of the vessel. In old chronic indurated ulcers, the lack of elasticity of the surrounding tissue prevents the vessel from retracting and hemorrhage is consequently persistent.

DIAGNOSIS

An adequate history, as in all medical conditions, is the most important factor in making a diagnosis of acute massive hemorrhage from a peptic ulcer. A past history of an acute peptic ulcer or indefinite digestive disturbances and the present history of hematemesis or melena together with signs of shock and anemia should always suggest bleeding from a peptic ulcer.

In 1939, Scudder[98] introduced a simple and accurate falling-drop method of determining the specific gravity of the blood, which can be carried out at the bedside as frequently as necessary to follow the course of shock. He has shown that in the case of shock from acute massive hemorrhage, there are definite and constant demonstrable changes in the quality of the peripheral capillary blood. The specific gravity falls from a normal value of 1.0566 in males and 1.0533 in females to 1.0400 and less in the presence of severe hemorrhage. The blood hematocrit reading is low and the plasma protein value falls. There is a marked decrease in the whole blood potassium level but an increase in the blood serum potassium level. Moon and associates[82] demonstrated that the blood coagulation time is shortened in the presence of severe bleeding. The correlation of these values will reveal the severity of the hemorrhage, the progress of the bleeding, and the response to treatment much more quickly and accurately than methods which we have previously had at our disposal. In the early critical stage of massive hemorrhage, the hemoglobin and red blood cell values lag considerably and do not accurately indicate the blood loss.[37, 84]

Hinton[54, 55] described a transfusion test for determining the necessity of operation in acute massive hemorrhage as follows. If after two blood transfusions of 500 c.c. each, the hemoglobin and blood pressure remain low, one may assume that a large vessel has been eroded and surgical intervention is indicated.

Barium may be given early by mouth and x-rays taken of the upper gastrointestinal tract as an aid in diagnosis.[25] The danger in this procedure is not in giving the barium but in the trauma to the viscera by manipulation under the fluoroscope.

The gastroscopic examination of a patient in the presence of acute massive hemorrhage is definitely contraindicated.[88, 95] Snell[102] reports

its use at the Mayo Clinic in determining the source of hemorrhage in chronic persistent bleeding from the upper gastrointestinal tract.

PROGNOSIS

Patients rarely die during the initial massive hemorrhage from peptic ulcers.[8, 9, 76, 107] Meulengracht[77] found that death occurred, on the average, eight days after the onset of the bleeding. Blalock[21, 22] has found experimentally that death in the presence of severe hemorrhage occurs more often from shock than from exsanguination. It is the opinion of many men that patients with severe bleeding peptic ulcers do not succumb from loss of blood alone, but rather from exhaustion, which is accentuated by the extreme insufficiency of food and drink.[8, 9, 68, 76, 77, 110, 111]

The mortality rate is extremely high in patients over 45 years of age.[6, 34, 56] Several authors report that hemorrhage in the female is less serious than in the male.[25, 26, 31] There is also an abrupt rise in the mortality rate after the second hemorrhage.[18, 19, 92]

The initial treatment instituted is one of the most important factors determining the prognosis. Many authors report in the literature remarkably low mortality rates with a prompt dietary medical management.

THERAPY

The treatment of acute massive hemorrhage from gastric and duodenal peptic ulcers is a complicated problem. There has been much written during the past decade concerning this phase of the disease. It is agreed that all such patients should be immediately hospitalized and attended by an expert internist and a competent surgeon. The patient should be placed promptly on an adequate dietary medical regime and every effort made within forty-eight hours to single out those cases which require surgical control of the hemorrhage.

The initial shock is combated by rest, quiet, warmth,[24] the administration of adrenal cortical extract,[50] morphine sedation sparingly,[76] and oxygen.[100, 112] Transfusions in the presence of active bleeding must be administered with care.

MEDICAL THERAPY

The time-honored medical treatment which had been almost universally accepted and employed until the past decade was the conservative starvation medical management. This regime consisted of a period of starvation of the patient up to several days, administration of large doses of morphine, complete immobilization, infusions of glucose, and transfusions of variable amounts of blood. The period of starvation was followed by the administration of minimal feedings of a bland diet in slowly increasing amounts, as illustrated by a progressive Sippy diet. Close analysis of the mortality statistics reported in the literature for

TABLE I

STARVATION REGIME

MORTALITY STATISTICS AS REPORTED IN LITERATURE

AUTHORS	YEAR	HOSPITAL	TOTAL CASES	DEATHS	MORTALITY (%)
Paterson	1924	London (collected)	1343	52	3.8
Paterson	1924	London (collected)	Acute massive		11.8
Lynch	1927	Montreal General	31	4	12.9
Ross	1930	Melborne	45	26	58.0
Hinton	1931	Bellevue	52	10	20.0
Mattison	1931	Sweden	---	--	7.0
Bulmer	1932	Birmingham General	467	48	10.7
Chiesman	1932	St. Thomas	191	48	25.0
Allen and Benedict	1933	Massachusetts Gen.	138	20	14.5
Mossberg	1933	Sweden	---	--	9.0
Aitken	1934	London	255	27	11.0
Burger and Hartfall	1934	Guy	117	21	18.0
Christensen	1934	Kommunenhospital	289	23	7.9
Frostad	1934	Norway	---	--	9.4
Hellier and Camb	1934	Leeds	202	26	13.0
Hendon	1935	Louisville	46	5	10.0
Westermann	1935	St. Luke's	50	10	20.0
Babey	1936	Guy	82	4	4.8
Goldman	1937	San Francisco	349	39	11.5
Jankelson and Siegel	1938	Boston City	189	18	9.0
Pfeiffer	1938	Larkenau and Abington Memorial	40	3	7.5
Browne and McHardy	1939	Touro Infirmary	40	4	10.0
Crohn and Lerner	1939	Mount Sinai	94	4	4.2
LaDue	1939	Minneapolis General	82	8	9.8
Marshall and Kiefer	1939	Lahey Clinic	108	5	4.6
Bergh, Hay, Trach	1940	U. of Minnesota Hospital	70	7	10.0
Bergh, Hay, Trach	1940	Collected Cases	2565	262	10.2
Welch and Yunich	1940	Albany	125	11	8.8
Bohrer	1941	Collected Cases	1008	124	11.3
Miller	1941	Collected Cases	5843	508	8.7
Rafsky and Weingarten	1942	Lenox and Beth Israel	271	30	11.0

this type of therapy reveals an astonishingly high mortality rate. The mortality rates, as listed in Table I, range from 4.2 to 58.0 per cent.

In 1906, Lenhartz[68] described a dietary treatment of 146 patients with bleeding peptic ulcer resulting in a mortality rate of 2.14 per cent. This report did not receive wide acceptance. Andresen,[8] in 1927, published a report of an entirely new method of management of bleeding peptic ulcers with prompt and fairly liberal feedings of a gelatin-water mixture administered at two-hour intervals. Unfortunately, he reported no statistical data to support the regime. In 1939, he reported a modified Andresen diet as follows: A 1000 calorie diet, consisting of gelatin combined with milk, cream, and glucose flavored with coffee, tea, chocolate, or vanilla, is prepared as a very palatable drink.[9] Six ounces of this formula are given every two hours for the first four days. On the fifth and sixth days egg, cereal, custard, jello, and ice cream are added and on the ninth day a regular modified ulcer diet is begun. At this time Andresen reported a mortality rate of 2.5 per cent for 120 patients with bleeding peptic ulcers treated by this method.

Meulengracht[76] made a tremendous impression upon the medical profession when he reported, in 1934, a mortality rate of 1.2 per cent for 251 cases of bleeding peptic ulcer treated with a pull puree, qualitatively and quantitatively balanced, diet. The original full puree diet as described by Meulengracht is as follows:

6:00 A.M. Tea, white bread, and butter
9:00 A.M. Oatmeal with milk, white bread and butter
1:00 A.M. Dinner of great variety (meat balls, boiled chops, omelet, fish balls, vegetable au gratin, mashed potatoes, tapioca pudding, etc.)
3:00 P.M. Cocoa
6:00 P.M. White bread, butter, sliced meats, cheese, and tea

This diet is supplemented by the administration of morphine sparingly, iron compounds, and transfusions as indicated. An antacid-antispasmodic mixture is prescribed as follows:

℞

Sodii Bicarbonatis } āā, gr. XV
Magnesii Subcarbonatis }
Extract Hyoscyami gr. LI

Sig.: One teaspoonful t.i.d.

The patients remain in bed two or three weeks and are discharged, symptom free, in five weeks. They are x-rayed at the end of this period and usually continue on the diet for several months. The chief merit of the Meulengracht diet lay in the reduction of the mortality rate rather than in an ultimate cure of the ulcer.

Mortality statistics reported with the use of the prompt and frequent feeding regime have been collected from the literature and are presented in Table II. The mortality rates are surprisingly low and range from 0.0 to 11.2 per cent. Of interest is the report of Woldman[111] of a mortality rate of 2.0 per cent employing a continuous intragastric drip of a solution of aluminum hydroxide. This regime was supplemented with two-hour interval feedings of a bland diet. There have been numerous variations of the diet but the Meulengracht and Andresen regimes depend upon the prompt and frequent feeding regardless of the diet. Thus, the type of diet is secondary to the promptness of the administration.

The factors responsible for the excellent results obtained by the immediate feeding regime are as follows:

1. The presence of food in the stomach diminishes the hunger contractions and permits blood clotting to occur in the base of the ulcer. Christensen[33] and Carlson[30] have shown conclusively that the fairly well-filled stomach is at all times relatively inactive in contrast to the vigorous activity of the empty stomach.

TABLE II

PROMPT FEEDING REGIME

MORTALITY STATISTICS AS REPORTED IN THE LITERATURE

AUTHORS	YEAR	HOSPITAL	TOTAL CASES	DEATHS	MORTALITY (%)
Lenhartz	1906	Eppendorf	146	3	2.14
Howard and Barry	1934	Omaha	12	1	8.3
Alder	1936	Konlonsepitals Aoran	40	0	0.0
Bernstein	1936	Jewish	28	0	0.0
Gubergritz	1936	University of Kiev	15	0	0.0
Gram	1936	Sundby	106	2	2.0
Lineberry and Issos	1937	Birmingham General	38	1	3.6
Witts	1937	St. Bartholomew	24	0	0.0
Boyd and Schlachman	1938	Metropolitan	15	0	0.0
Herlihy	1938	Lewisholm	3	0	0.0
Miller and Elsom	1938	Collected Cases	509	9	1.8
Andresen	1939	Long Island College	120	3	2.5
Barnes	1939	----------	30	0	0.0
Browne and McHardy	1939	Touro Infirmary	37	1	2.7
Chasnoff, Schwartz, and Leibowitz	1939	Beth Israel	21	1	4.8
D'Albana	1939	Long Island College	53	1	1.8
Graham, Kerr, and Alexander	1939	Western Infirmary	44	0	0.0
Jones	1939	St. Bartholomew	50	1	2.0
LaDue	1939	Long Island College	81	--	1.3
Meulengracht	1939	Bispebjirg	491	10	2.0
Crohn and Lerner	1939	Mt. Sinai	23	2	8.6
Vendt	----	----------	288	7	2.4
Scott	1940	Western Infirmary	60	2	3.3
Allen	1941	Massachusetts Gen.	80	9	11.2
Drevs and Voss	1941	----------	57	2	3.5
Emery	1941	Peter Bent Brigham	36	2	5.5
McMillan	1941	Winston-Salem	12	0	0.0
Miller and Nicholson	1941	Univ. of Pennsylvania	32	1	3.0
Miller and Nicholson	1941	Collected in Literature			
		Strict Meulengracht	871		
		Bland Diet	525	--	3.1
Mayer and Lightbody	1941	Receiving	133	2	1.5
Schiff	1941	Cincinnati General	---	--	6.0
Scott	1941	Western Infirmary	60	2	3.3
Segal, Scott, and Stevens	1941	Strong Memorial	35	1	3.0
Woldman	1941	St. Luke's	144	3	2.0
Turnbull and Sagi	1939	Evanston	80	2	2.5
Rafsky and Weingarten	1942	Lenox, Beth Israel			
		Meulengracht	39	4	10.3
		Sippy Diet	34	1	2.9

2. The presence of food in the stomach increases the tone and the stomach maintains a constant and continuous pressure on its contents. Miller and Nicholson[80] suggest that this increased intragastric and intraduodenal pressure tends to close an open vessel and promotes clot formation.

3. Gastric secretions are fixed by the foods, preventing the dissolving of the clot.[8, 12, 26, 32, 76]

4. A high protein diet replaces blood protein lost by the hemorrhage.[8, 9, 73, 76, 110]

5. A high carbohydrate diet protects the liver and prevents acidosis.[32, 77]

6. Adequate vitamin C promotes rapid healing of the ulcer and prevents oozing in the posthemorrhagic state.[77, 88, 99]

7. Regeneration of blood occurs much more rapidly with the administration of food. This was conclusively shown by Schiødt.[96]

8. The patient's morale is raised and he is calm, composed, comfortable, and cooperative.[32, 38, 53, 74, 76, 91, 94, 110]

9. The convalescence is shortened.[74, 76, 77, 97, 110]

Transfusions are an important part of the therapeutic armamentarium. Indications for immediate transfusion are extreme shock, marked air hunger and anoxemia, a hemoglobin level below 40 per cent, and a blood pressure below 90 mm. of mercury. There are reports in the literature both for and against the routine administration of blood early in the presence of severe bleeding, but there is a general tendency toward conservatism. In 1935, Marriott and Kekwich[70] proposed the use of massive transfusions as a continuous drip. They have given as much as 3000 to 4000 c.c. of blood over a period of a few days. This is made easier in many hospitals since the advent of the blood bank. Wood,[113] Black and Camb,[17] and Jones,[61] state that slow massive transfusions merely tend to restore gradually the blood pressure to normal level and do not cause increased bleeding. Most reports on the treatment of acute massive hemorrhage advise considerable care in the use of the blood transfusion and suggest that small amounts of 200 to 300 c.c. be administered.[33, 34, 35, 59, 99] Crohn and Lerner[34] feel that the low blood pressure is an excellent natural mechanism for promoting clot formation and should not be unduly disturbed by large transfusions. Shulman and Glass,[101] Kilduffe and DeBakey,[62] and others[4, 5, 6] hold that blood transfusions exert a hemostatic and coagulative action and that the so-called danger of increasing the blood pressure and "blowing-out" a blood clot is a fallacious belief. Also in this connection Allen[4] states, "We have seen patients die from the lack of blood but in no instance have we seen transfusions responsible for fatal hemorrhage."

Andresen in discussing the use of an ice bag has this to say,[9] "As far as the ice bag is concerned, its only advantage, the prevention of undue motion on the part of the patient, in an effort at balancing it on the abdomen, is more than overcome by the disadvantage of wakefulness induced by fear of its being dislodged during sleep."

SURGICAL THERAPY

During the past decade there has been a definite trend among surgeons toward the advocacy of early and radical operative treatment for bleeding peptic ulcers. Finsterer[41] was the first surgeon to advise immediate surgical intervention in acute massive hemorrhage. Working under optimal conditions and operating early, before forty-eight hours had elapsed, he reported a mortality rate of 5.1 per cent in seventy-eight cases. Operating upon seventy-four patients for the same disease after forty-eight hours had elapsed, he obtained a mortality rate of 29.7 per

cent. Therefore, Finsterer advocates early operation, before forty-eight hours have passed, in order to insure a reasonable mortality rate. Gordon-Taylor,[44, 45] reporting a series of thirty-two patients treated under similar conditions, had a mortality rate of 19 per cent. In a series of 254 operations for bleeding peptic ulcer, not adequately classified as to acute massive hemorrhage or chronic persistent hemorrhage, Walters and Cleveland[105] of the Mayo Clinic reported a mortality rate of 7.4 per cent.

There is a great deal of indecision as to the accepted conditions and indications to be met before surgical intervention is undertaken. Graham,[47] feels that, given a patient over 50 years of age, who has a hemoglobin level below 50 per cent, operation should be seriously considered. It is generally agreed that patients under 50 years of age have an excellent prognosis for recovery from hemorrhage on a medical management.[4, 10, 11, 48, 57, 103, 107] Graham[47] states that a single massive hemorrhage in a young patient is not sufficient justification for operation. Lahey,[65] Balfour,[10] and Bevan,[16] reserve surgery for those cases of a decisive medical failure or for those with associated complications which in themselves are definite surgical indications.

Rankin and associates[89] have formulated a group of conditions to be fulfilled before surgery is undertaken. These conditions are as follows: (1) A massive hemorrhage occurring in a known peptic ulcer patient over 50 years of age; (2) a massive hemorrhage occurring in a known peptic ulcer of long standing which has failed to respond to careful continuous medical treatment; (3) a massive hemorrhage following one or more previous episodes of severe bleeding from a peptic ulcer; and (4) when a massive hemorrhage from a known ulcer of long standing or in an arteriosclerotic patient fails to respond to one or more transfusions but shows evidence of continuous or repeated bleeding.

Concerning surgery for bleeding peptic ulcers, Meulengracht says,[77] "I consider a mortality rate of 1 or 2 per cent on dietary medical management makes the question unreal to me and relieves me of the responsibility of having to decide in an individual case whether operation is advisable or not." Holman[56] and Rankin and associates[89] feel that the routine operative treatment of all bleeding peptic ulcers is impractical and not indicated, but in spite of the excellent results obtained on dietary medical management, there remains a small group of patients in which operative intervention is indicated. Holman[56, 57] considers the indications for early operation to be (1) an immediate recurrent or persistent bleeding after complete bed rest and (2) a hemorrhage beginning while the patient is receiving adequate medical treatment in the hospital. Wangensteen[107] awaits objective proof that those who attempt the surgical arrest of hemorrhage from a bleeding ulcer are able to perform such procedures with a reasonable mortality.

The mortality statistics for surgical treatment of bleeding peptic ulcers as reported in the literature have been compiled in Table III. In

comparing the mortality rates for surgical treatment with those obtained on adequate dietary medical management, it can be assumed that the safest treatment for the patient in any community, and especially where a competent surgeon is not available, is the prompt dietary medical regime.

The various surgical procedures employed will only be mentioned and not discussed. The operation of choice is partial gastrectomy with removal of the ulcer.[41, 45, 47, 104, 106, 107, 108] This prevents subsequent hemorrhage which frequently follows other more conservative operations. Other operations which have been advocated are the transduodenal ligation of the eroded vessels, anterior gastroduodenostomy, and excision of the gastric ulcer, with or without gastroenterostomy.

TABLE III

SURGICAL TREATMENT

MORTALITY STATISTICS AS REPORTED IN LITERATURE

AUTHORS	YEAR	HOSPITAL	TOTAL CASES	DEATHS	MORTALITY (%)
Hinton	1931	Bellevue	---	--	20.0
Cullinan and Price	1932	St. Bartholomew	---	--	72.0
Aitken	1934	London	21	7	33.3
Gordon-Taylor	1935	Middlesex	32	6	19.0
Westermann	1935	St. Lukes	42	13	32.5
Hurst and Ryle	1937	New Lodge Clinic	3	3	100.0
Jankelson and Siegel	1938	Boston City	11	3	27.0
Pfeiffer	1938	Larkenau and Abington Memorial	22	5	22.7
Browne and McHardy	1939	Touro Infirmary	14	3	21.4
Crohn and Lerner	1939	Mount Sinai	75	20	26.6
Finsterer	1939	Allgemeines Krankenhaus			
		Before 48 hours	78	4	5.1
		After 48 hours	74	22	29.7
Holman	1940	New York Hospital	45	6	13.0
Bohrer	1941	Knickerbocher and collected cases			
		Gastrectomy	112	20	18.0
		Other operations	48	17	35.4
Miller	1941	Collected cases	383	--	28.0
Walters and Cleveland	1941	Mayo Clinic	254	19	7.4

A REVIEW OF 284 CASES OF BLEEDING PEPTIC ULCER ADMITTED TO HARPER HOSPITAL, 1931 TO 1941

All cases of bleeding gastric and duodenal peptic ulcers, the acute massive hemorrhage, and the moderately severe hemorrhage, entering Harper Hospital between the years 1931 and 1941 have been reviewed. All patients were classified as having acute massive hemorrhage if they entered the hospital in shock, gave history of hematemesis or melena, had a red blood cell count of three million or less and a hemoglobin level of 50 per cent or less. The statistical data compiled from the charts of these 284 patients admitted with bleeding peptic ulcers is contained in Table IV.

TABLE IV

COMPILED DATA OF 284 CASES BLEEDING PEPTIC ULCER

(HARPER HOSPITAL, 1931 TO 1941)

YEAR	TOTAL CASES	SEX	OVER AGE OF 40 YEARS	CLASSIFICATION		TYPE OF ULCER	PREVIOUS BLEEDING	TREATMENT			CONVALESCENCE (DAYS)	DEATH
				MASSIVE	MILD			STARV.	FEED.	SURG.		
1931	12	3 F. 9 M.	5	8	4	7 Duo. 4 Gast.	9	8	4 Sippy	1	Food 12 Star. 18	0
1932	27	5 F. 22 M.	14	19	8	17 Duo. 8 Gast.	20	20	7 Sippy	4	Food 19 Star. 18	4
1933	19	4 F. 15 M.	11	17	2	7 Duo. 7 Gast.	13	16	3 Sippy	0	Food 13 Star. 14	2
1934	25	2 F. 23 M.	14	16	9	16 Duo. 5 Gast.	18	15	10 Sippy	3	Food 9 Star. 16	2
1935	18	4 F. 14 M.	15	15	3	10 Duo. 5 Gast.	14	13	5 Sippy	1	Food 18 Star. 16	4
1936	16	4 F. 12 M.	11	12	4	7 Duo. 8 Gast.	14	11	5 Sippy	0	Food 15 Star. 14	2
1937	30	9 F. 21 M.	18	25	5	17 Duo. 18 Gast.	21	23	5 Sippy 2 Meul.	1	Food 8 Star. 15	4
1938	13	1 F. 12 M.	9	10	3	8 Duo. 3 Gast.	12	9	4 Sippy	1	Food 17 Star. 10	1
1939	37	7 F. 30 M.	30	31	6	24 Duo. 11 Gast.	22	23	11 Sippy 3 Meul.	1	Food 15 Star. 18	1
1940	41	6 F. 35 M.	32	25	16	30 Duo. 10 Gast.	34	17	21 Sippy 3 Meul.	1	Food 16 Star. 16	0
1941	46	9 F. 37 M.	30	30	16	31 Duo. 11 Gast.	30	25	12 Sippy 9 Meul.	3	Food 14 Star. 17	2
Total	284	54 F. 230 M.	189	208	76	173 Duo. 90 Gast.	207	180	104	16	Food 14 Star. 16	22

There were 208 patients who suffered from acute massive hemorrhage and 74 patients who had mild or chronic bleeding from either gastric or duodenal peptic ulcers. The distribution of the 208 cases is shown graphically in Fig. 1. There were seventy cases of acute massive hemorrhage treated by a prompt and frequent feeding regime. Eleven patients received the Meulengracht diet and the remainder received the Sippy fluid diet or a soft diet. There were 138 patients treated by the strict starvation regime. Seven patients with acute massive hemorrhage were operated upon with one death.

During the eleven-year period, 1931 to 1941, there were twenty-two deaths from bleeding gastric and duodenal peptic ulcers treated at Harper Hospital. One death was due to surgery; a pyloroplasty was performed and a fatal peritonitis developed. There were twenty-one deaths in those patients treated medically. These deaths are analyzed in Table V.

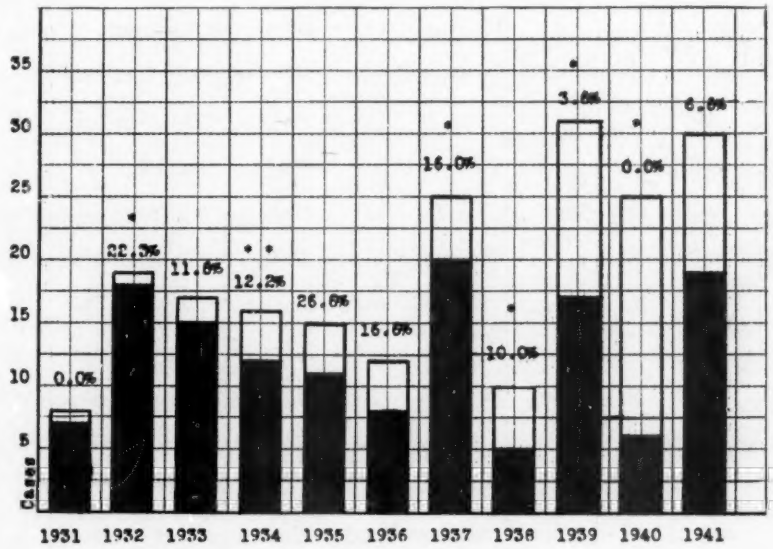

Fig. 1.—Distribution of 208 cases of acute massive hemorrhage.
Cases treated by prompt feeding (70 patients).
Cases treated by starvation regime (138 patients).
* Indicates each patient treated surgically (7 patients).
% Mortality rate yearly on medical management.

After reviewing the data as compiled in the last three tables, the following conclusions can be drawn.

1. There were twenty-one deaths in the entire series of 284 cases of bleeding peptic ulcers. All deaths occurred in the presence of acute massive hemorrhage. The mortality rate for the 208 cases of acute massive hemorrhage was 10.0 per cent.

2. Seven patients with acute massive hemorrhage were submitted to surgery. There was one death, resulting in a surgical mortality rate

TABLE V

ANALYSIS OF 22 DEATHS FROM ACUTE MASSIVE HEMORRHAGE HARPER HOSPITAL (1931 TO 1941)

YEAR	AGE	SEX	TYPE OF ULCER	BLEEDING	CAUSE OF DEATH	TREATMENT	HOSPITALIZATION PERIOD
1932	48	F.	Duo.	?	Acute Massive Hem.	Starvation Diet	6 Days
1932	50	M.	?	Primary	Acute Massive Hem.	Starvation Diet	11 Days
1932	58	M.	Duo.	Primary	Acute Massive Hem.	Starvation Diet	5 Days
1932	38	M.	?	Primary	Acute Massive Hem.	Starvation Diet	11 Days
1933	70	M.	Duo.	Secondary	Acute Massive Hem.	Starvation Diet	1 Day
1933	49	M.	Gast.	Primary	Acute Massive Hem.	Starvation Diet	11 Days
1934	34	M.	Duo.	Primary	Acute Massive Hem.	Starvation Diet	13 Days
1934	31	M.	Duo.	Secondary	Pyloroplasty with peritonitis	Starvation Diet	17 Days
1935	50	M.	Duo.	Primary	Acute Massive Hem.	Sippy Diet	20 Days
1935	46	M.	Duo.	Primary	Acute Massive Hem.	Starvation Diet	6 Days
1935	52	M.	?	Primary	Acute Massive Hem.	Starvation Diet	3 Days
1935	56	F.	Gast.	Primary	Acute Massive Hem.	Starvation Diet	26 Days
1936	59	F.	Gast.	Primary	Acute Massive Hem.	Starvation Diet	4 Days
1936	52	M.	Gast.	Primary	Acute Massive Hem.	Starvation Diet	6 Days
1937	31	F.	Gast.	Primary	Acute Massive Hem.	Starvation Diet	5 Days
1937	64	F.	?	Primary	Acute Massive Hem.	Starvation Diet	1 Day
1937	40	M.	Gast.	Secondary	Acute Massive Hem.	Starvation Diet	59 Days
1937	47	F.	Gast.	Primary	Acute Massive Hem.	Starvation Diet	8 Days
1938	50	M.	Duo.	Primary	Acute Massive Hem.	Soft Diet (few feedings)	4 Days
1939	62	M.	Gast.	Primary	Acute Massive Hem.	Starvation Diet	2 Days
1941	66	F.	Duo.	Primary	Acute Massive Hem.	Starvation Diet	3 Days
1941	66	M.	?	Primary	Acute Massive Hem.	Starvation Diet	8 Hours
22 Patients	17 over 45 years of age	7 F. 15 M.	9 Duo. 8 Gast.	18 Primary 3 Secondary	1 Surgical death	2 Feeding 20 Starvation	Av. 10 Days Mean 6 Days

of 14.0 per cent. There were fifteen patients operated upon in the entire series with one death. Thus, the total surgical mortality rate was 7.0 per cent for both the acute and moderate hemorrhages.

3. Two deaths occurred in a series of seventy patients with acute massive hemorrhage treated by a prompt feeding regime. One of these patients received very little food as he entered the hospital in the

evening and was not fed until the next morning. However, the two deaths gave a mortality rate of 2.8 per cent on immediate feeding management.

4. Nineteen deaths occurred in a series of 138 patients with acute massive hemorrhage treated by a starvation regime, resulting in a mortality rate of 13.7 per cent.

5. Seventeen deaths occurred in patients over 45 years of age, an 80 per cent incidence.

6. There were no deaths from the initial massive hemorrhage. Eighteen patients who expired from acute massive hemorrhage gave no history of previous episodes of bleeding; conversely, only three patients who died gave a history of previous bleeding.

7. The average period of hospitalization of the fatal cases was from six to ten days, corresponding with the figure reported by Meulengracht.[76]

8. This condition is four times as common in the male as in the female. However, there were seven deaths in the group of 54 female patients with acute massive hemorrhage, giving a mortality rate of 13.0 per cent. Fifteen men died in the group of 230 male patients. The mortality rate for men is 6.5 per cent, much less than for women.

9. Duodenal ulcers are more often the source of the hemorrhage than are gastric ulcers. The mortality rate is higher for acute hemorrhage from gastric peptic ulcers than for duodenal peptic ulcers.

10. There has been a marked increase in the number of patients with acute massive hemorrhage from peptic ulcers admitted to Harper Hospital during the past three years.

11. The trend in treatment for acute massive hemorrhage from peptic ulcer at Harper Hospital is definitely in favor of the prompt and frequent feeding management.

SUMMARY

In acute massive hemorrhage from gastric and duodenal peptic ulcers, the mortality rate is markedly lowered by the prompt and frequent administration of an adequate dietary medical regime.

Of 284 patients admitted to Harper Hospital from 1931 to 1941 with the diagnosis of bleeding peptic ulcer, there were 208 patients with acute massive hemorrhage.

The mortality rate for seventy patients with acute massive hemorrhage treated by a prompt and frequent feeding regime was 2.8 per cent.

The mortality rate for 138 patients with acute massive hemorrhage from peptic ulcer treated by a starvation regime was 13.7 per cent.

Seven patients with acute massive hemorrhage from peptic ulcer were operated upon with one death. Thus, the surgical mortality rate in the presence of acute hemorrhage was 14.0 per cent for a very small group of cases.

There is no proof, as yet, that those who attempt the surgical arrest of acute massive hemorrhage from a peptic ulcer are able to do so with a reasonable mortality.

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Book Reviews

History and Evolution of Surgical Instruments. By C. J. S. Thompson, Royal College of Surgery, London, with a foreword by Chauncey D. Leake. Pp. 113, illustrations 115, New York, N. Y., 1942. Schuman's.

Professor Thompson, a well-known English medical historian, sets forth in this monograph a brief recital of what is known concerning the development of surgical instruments. The monograph is particularly valuable now, in that the author has surveyed the fine collection of surgical instruments which, before the Nazi aerial bombardments of London, contributed one of the most remarkable historical collections of surgical instruments extant. That collection has now been largely destroyed. It is particularly fortunate, therefore, that this survey of the author was well under way before that grim act of destruction occurred.

It is interesting to observe in this monograph the development of various instruments. Those instruments like the saw used by cabinetmakers still were well developed 100 years and more ago, resembling very closely those used by modern surgeons; similarly, the instruments used for trepanation of the skull, having as antecedents the brace and drill of the cabinetmaker, early assumed a form not unlike that of modern instruments used for the same purpose. When the surgeon had to do his own improvising, it is painful to observe how slow his progress was as witness the slow development of the artery forceps and instruments for dissection. The story of the development of the scalpel and the operating table reflects quite directly the role of the surgeon's activity. Prior to anesthesia and aseptic surgical practices, the point of the scalpel received the greatest notice from surgical innovators; thereafter, the blade poised for cutting became the chief object of concern. The author concludes with the suggestion that more recent developments in the facilities of the surgeon in the operating room "are a story in themselves"—a chapter with which he does not wish to deal.

The book is one which should interest all surgeons, with a historical sense, who desire to know something of the manner in which his instrumentarium came into being.

Intestinal Obstructions: A Physiological and Clinical Consideration with Emphasis on Therapy; Including Description of Operative Procedures. By Owen H. Wangensteen, B.A., M.D., Ph.D., Professor of Surgery of the University of Minnesota and Surgeon-in-Chief of the University of Minnesota Hospital, Minneapolis. Ed. 2. Cloth. Pp. 484, with 143 illustrations, of which 82 are newly introduced in this edition. Springfield, Ill., 1942, Charles C Thomas, Publisher. $7.00.

The second edition of Dr. Wangensteen's book, which is considerably larger than the first, remains a useful monograph and compendium of information on intestinal obstruction. The author's own important contributions to the subject are many.

The discussion of the pathologic physiology of intestinal obstruction, with particular stress on the author's "mechanistic" interpretation, is excellent. References are plentiful, well chosen, and separately grouped after each chapter.

The use of indwelling tubes is fully discussed. The author permits himself to say that while he has abandoned the duodenal tube for the Miller-Abbott tube,

he has noticed no attributable reduction in mortality. When mechanical obstruction of a strangulating character is known to be present, he advises against sole reliance on the tube; whereas it might be more safely put that one should depend solely on the tube only when it is known that mechanical obstruction is not present. The differentiation of the types of obstruction is didactic and oversimplified.

This reviewer is grateful for Dr. Wangensteen's attack on two time-honored surgical maxims repeated from text to text and lecture to lecture. He maintains, with good reason, that in acute appendicitis with peritonitis death is not due to paralytic ileus but to infection. The old dictum that high intestinal obstruction is more lethal than low is shown to date from the period before adequate fluid replacement. A patient with high obstruction can be carried along, with replacement of fluids, long after a patient with low small intestinal obstruction has succumbed to the effects of distention and pressure in a long stretch of bowel.

Many of the sections on special types of obstruction are interesting. It is a little hard to understand the frequent reference to obstruction of the intestine by gallstones.

The use of enterostomy in surgical management of intestinal obstruction is very strongly stressed and recommended, an attitude which is at variance with present-day surgical practice in most clinics.

Epilepsy and Cerebral Localization. By Wilder Penfield, M.D., D.Sc., and T. C. Erickson, M.D., M.A., M.Sc., McGill University. Pp. 623, with 163 illustrations. Charles C Thomas, Publisher. Springfield, Ill., 1941. $8.00.

This well-written, encyclopedic treatise on epilepsy contains material from the authors, many contributions concerning epilepsy published in the periodic literature, and, in addition, a most comprehensive review of the literature on epilepsy. Focal epilepsy is the type which the authors have most extensively investigated, but all types of epilepsy are fully discussed in this book.

Since the investigation of the mechanism and treatment of focal epilepsy has led the authors to extensive study of cerebral localization, it is natural that the whole subject of functional localization in the cerebral cortex, its history and present status should be reviewed here. They have had the most extensive experience with observations in stimulation of the cerebral cortex of conscious patients.

This book is a most comprehensive treatise on the history, mechanism, etiology, surgical treatment, medical treatment, and psychology of the epileptic patient.

An abundance of illustrative case reports are given in detail. The efficient arrangement which the authors have for taking photographs in the operating room is reflected in the many photographs of exposed cortex. However, the diagrams which supplement these photographs are equally, if not more, helpful to the reader.

The large amount of original investigation reported and the laborious compilation and inclusion of information from the literature should make this book one of lasting value.

Synopsis of Pathology. By W. A. D. Anderson, M.A., M.D., Pp. 661, with 294 illustrations, and 17 color plates. St. Louis, 1942, C. V. Mosby Company.

This book is one of a recent series of synopsis of various subjects related to the study of medicine. The value of any one of these condensed presentations will depend upon two main points, namely: (1) the completeness with which the author has covered the subject to include the various phases of the subject under discussion and (2) the brevity with which each phase is presented.

Dr. Anderson presents a condensed discussion of the pathologic changes occurring in disease, as well as a discussion of the pathologic processes occurring in these same diseases as related to their application to clinical medicine. The very nature and purpose of this book precludes the possibility of completeness of discussion in any of the subjects presented. However, for the most part, the author has not, apparently, sacrificed clarity of description for brevity of presentation.

The descriptions and discussions are supplemented by a wealth of black and white photographic plates of the gross as well as the microscopic changes occurring in the different parts of the body. With a few exceptions, the detail of these photographs is excellent and because of this they greatly augment the value of the brief descriptions to which they refer. In addition to the innumerable photographs mentioned, there are seventeen color plates.

As mentioned in the preface, the bibliography is very incomplete. Unfortunately, this is unavoidable in such a condensation of so vast a subject. However, the references, which are listed, are of recent date and should form a basis for further investigation of any subject discussed.

Textbook of Surgery. By American authors, edited by Frederick Christopher, B.S., M.D., F.A.C.S. Ed. 3. Pp. 1764, with 1538 illustrations on 771 figures. Philadelphia and London, 1942, W. B. Saunders Company. $10.00.

The first edition appeared in 1936 and, as the editor states, "The dominant plan of this textbook is to give the student a concise presentation of surgery which is characterized by the maximum authority. The contributors, whose painstaking work has made this book possible, have been chosen because of their outstanding ability in the subjects which they present. The subject matter contains the tested and accepted present-day principles of surgery. Etiology, pathology, and diagnosis have properly been stressed, and the correct surgical treatment has been carefully described." A second edition was published in 1939.

The present publication is an up-to-date, practical treatise on surgery which follows the design of previous editions. There are several new sections, including one on war injuries, pruritus and hemorrhoids, abnormalities of the thymus, compound fractures, coccidiodal granuloma, and patent ductus arteriosus. Other sections have been completely revised or rewritten. The utilization of a great number of collaborators, writing upon the field of their special interests, is the distinctive feature of this volume; consequently, it carries the advantage of more authoritative and precise information than texts of different plan and format. Throughout the text, various contributors have indicated the many applications of the sulfonamide group of drugs and the beneficial results which may be expected. Pertinent references to literature are appended at the end of each discussion for readers who wish to study the subject more extensively.

This book is generally eminently practical, it is fundamental enough for students and is not too brief as a reference book for practitioners. There is little that one can criticize. The illustrations, both diagrams and photographs, are well chosen. As is so often the case, there is no lack of definitive information concerning the mortality as well as the results of surgical intervention.

To all physicians engaged in the practice of surgery this valuable book is seriously and enthusiastically recommended.

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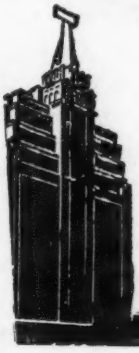

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